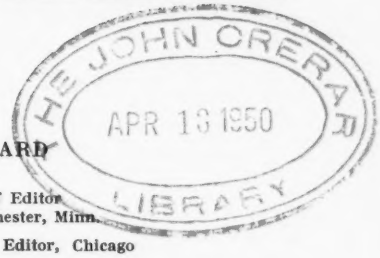
VOLUME 61 NUMBER 4

ARCHIVES
OF
DERMATOLOGY AND SYPHILOLOGY



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APRIL 1950

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $12.00

Entered as Second Class Matter Oct. 30, 1917, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

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COMPARATIVE ANALYSIS OF THE MUCOCUTANEOUS-OCULAR SYNDROMES

Report of Eleven Cases and Review of the Literature

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AND
FRED R. McCRUMB Jr., M.D.
BALTIMORE

FREQUENT reference has been made in the literature relative to a syndrome of unknown etiology consisting of lesions occurring in the eyes and mouth and on the genitalia. This syndrome has been called by various authors Behcet's disease, Stevens-Johnson disease, Reiter's disease and ectodermosis erosiva pluriorificialis. A critical review of the features of these symptom groups as recorded by the various authors indicates the pronounced similarity which exists between all of them and suggests that according to the modern concept they are all probably variants of the same disease entity, erythema multiforme exudativum. It is our intention to attempt to clarify this contention by discussing each so-called entity individually, then by making a comparison of them all and finally by presenting a report on 11 cases.

BEHCET'S DISEASE

In 1937, Behcet [1] gave his original description of a disease picture in which there were associated genital, oral and ocular lesions. At that

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Read before the Section on Dermatology and Syphilology at the Ninety-Eighth Annual Session of the American Medical Association, Atlantic City, N. J., June 8, 1949.

1. Behcet, H.: Ueber rezidivierende, aphthöse, durch ein Virus verursachte Geschwüre am Mund, am Auge, und an den Genitalien, Dermat. Wchnschr. **105**:1152, 1937; (*b*) Kurze Mitteilung über Fokalsepsis mit aphthösen Erscheinungen an Mund, Genitalien und Veränderungen an den Augen, als wahrscheinliche Folge einer durch Virus bedingten Allegemeininfektion, ibid. **107**:1037, 1938; (*c*) Considérations sur les lésions aphtheuses de la bouche et des parties génitales ainsi que sur les manifestations oculaires d'origine probablement parasitaire et observations concernant leur foyer d'infection, Bull. Soc. franç. de dermat. et syph. **45**:420, 1938; (*d*) A propros d'une entité morbide due probablement à un virus spécial donnant lieu à une infection généralisée se manifestant par des poussées récidivantes en trois régions principales et occasionnant en particulier des iritis répétés, ibid. **46**:674, 1939; (*e*) Some Observations on the Clinical Picture of the So-Called Triple Symptom Complex, Dermatologica **81**:73, 1940.

time he expressed the opinion that he had discovered a new disease entity and stated the firm belief that the disease was caused and maintained by a focus of infection and had a virus etiology. In his first case he found inclusion bodies, a finding which has never been verified by any investigator who has since reported on this so-called "triple symptom complex." The latter term was first applied to the entity by

TABLE 1.—*Behcet's Disease*

Original criteria for diagnosis

1. Aphthous ulcers in the mouth
2. Aphthous ulcers on the genitalia
3. Episcleritis and erosions on cornea

Symptoms added in subsequent reports

Ocular signs

1. Iritis with hypopyon
2. Conjunctivitis
3. Keratitis
4. Retinitis
5. Uveitis
6. Phlyctenules
7. Iridocyclitis
8. Choroiditis
9. Symblepharon
10. Neuroretinitis hemorrhagica

Genital lesions

1. Herpes-like vesicles
2. Deep ulcerations

Oral lesions

1. Ulcers on lips, tongue and buccal mucosa

Cutaneous lesions

1. Erythema nodosum
2. Furuncles
3. Pyoderma
4. Seborrheic eczema
5. Acne-like eruption
6. Erythema multiforme
7. Hyper-reactivity to intradermal tests

Joint signs

1. Arthritis
2. Rheumatic pain

Behcet in 1940. His reports included 6 patients. It is interesting to note that, although he has been given credit for discovering a new disease syndrome, Bluthe,[2] Adamantiades,[3] Dascalopoulos[4] and Whit-

2. Bluthe, L.: Zur Kenntniss des recidivierenden Hypopyons, Inaug. Dissert., Heidelberg, D. Strauss, 1908.

3. Adamantiades, B.: Sur un cas d'iritis à hypopion récidivant, Ann. d'ocul. **168**:271, 1931.

4. Dascalopoulos, N.: Sur deux cas d'uvéite récidivante, Ann. d'ocul. **169**:387, 1932.

well [5] had described a similar symptom complex years prior to Behcet's original report. In order for a case properly to be classified as an example of the "triple symptom complex," there should be exhibited in it all three of the manifestations; however, Curth [6] stated that it is not necessary for all three signs to be present simultaneously, and 1 of her patients had lesions only in the mouth and on the vulva. Patients in whom there were ocular and genital lesions, ocular and oral lesions or oral and genital lesions were considered by Franceschetti and Valerio,[7] Cavara,[8] Berlin [9] and Dascalopoulos [4] as having Behcet's disease syndrome, despite the fact that only two components of the triple symptom complex were present. The various manifestations of the disease syndrome are given in table 1.

Ocular Lesions.—The chief clinical picture in the eye is that of chronic recurrent iritis with hypopyon, which occasionally becomes severe enough to cause blindness. The ocular signs usually begin in one eye, but both eyes become affected as the disease process progresses. Among the forms of ophthalmic diseases which have been reported are conjunctivitis,[10] keratitis,[9] episcleritis,[10] corneal ulcerations,[1] retinitis,[10] uveitis,[11] phlyctenules,[9] iritis,[12] iridocyclitis,[10] choroiditis,[13] symblepharon,[14] neuroretinitis hemorrhagica,[9] and iritis with hypopyon.[15] In

5. Whitwell, G. P. B.: Recurrent Buccal and Vulval Ulcers with Associated Embolic Phenomena in the Skin and Eye, Brit. J. Dermat. **46**:414, 1934.

6. Curth, H. O.: Recurrent Genito-Oral Aphthosis and Uveitis with Hypopyon (Behcet's Syndrome): Report of Two Cases, Arch. Dermat. & Syph. **54**:179 (Aug.) 1946.

7. Franceschetti, A., and Valerio, M.: L'uveite recidivante (ad ipopion) manifestazione parziale di una sindrome muco-cutaneous-oculare, Rassegna ital. d'ottal. **9**:1, 1940.

8. Cavara, V.: Ueber ein besonderes Syndrom, gekennzeichnet durch rezidivierende Hypopyoniritis, verbunden mit Geschwüren des Mundes und der Geschlechtsteile und mit Hautausschlägen, Klin. Monatsbl. f. Augenh. **104**:629, 1940.

9. Berlin, C.: Behcet's Syndrome with Involvement of the Central Nervous System, Arch. Dermat. & Syph. **49**:227 (April) 1944.

10. Behcet.[1] Berlin.[9]

11. (*a*) Berlin. (*b*) Jensen, T.: Sur les ulcérations aphtheuses de la muqueuse de la bouche et de la peau génitale combinées avec les symptômes oculaires (Syndrôme Behcet), Acta dermat.-venereol. **22**:64, 1941.

12. (*a*) Jensen.[11b] (*b*) Ephraim, H.: Triple Symptom Complex of Behcet: Report of a Case, Arch. Dermat. & Syph. **50**:37 (July) 1944.

13. Curth.[6] Ephraim.[12b]

14. Knapp, P.: Beitrag zur Symptomatologie und Therapie der rezidivierenden Hypopyoniritis und der begleitenden aphthösen Schleimhauterkrankungen, Schweiz. med. Wchnschr. **71**:1288, 1941.

15. (*a*) Berlin.[9] (*b*) Curth.[6] (*c*) Cavara.[8] (*d*) Ephraim.[12b] (*e*) Franceschetti and Valerio.[7] (*f*) Schultheiss-Linder, H.: Beitrag zur Symptomatologie und Therapie der die rezidivierende Hypopyoniritis begleitenden Genitalulzera und über die Beziehung derselben zum Ulcus vulvae acutum Lipschütz und zu den

(Footnote continued on next page)

view of the fact that this disease is of unknown etiology and there is no specific treatment, the prognosis of the lesions of the eye becomes more serious with repeated attacks, especially if the patient acquires iritis with hypopyon. It is interesting to note that the patients of Behcet's original cases had only episcleritis and erosions on the cornea and did not have iritis with hypopyon.

Genital Lesions.—The genital lesions, as reported by the various authors, varied from groups of herpes-like vesicles to superficial and deep ulcerations which appeared on the penis, scrotum or the inner sides of the thighs in the male and on the labia majora in the female. These lesions were painful and interfered with walking. In Curth's [6] female patient the onset of the genital ulcers was frequently marked by systemic symptoms, with chills and high fever, but in her male patient the lesions appeared without any premonitory systemic signs.

Oral Lesions.—The chief clinical manifestations in the mouth consisted of painful, aphthous ulcers. These lesions were discrete, variously sized and shaped and might be found on the lips and tongue and gingival and buccal mucosa.

Cutaneous Lesions.—A variety of skin lesions have been associated with this particular group of symptoms. Erythema nodosum [16] was by far the commonest recurring manifestation on the skin and in fact was present in 2 of Behcet's own original cases. Seven other reports also mentioned this entity. In the other reports 2 patients had furuncles,[17] 1 a pyoderma [18] and 1 seborrheic eczema.[8] One of the case reports mentioned an acne-like eruption, and 3 persons had typical lesions of erythema multiforme.[19]

Other Observations.—Jensen [11b] and Ephraim [12b] noted a pronounced hyperreactivity of the skin to many intradermal tests and controls.

Vitaminen des B-Komplexes, Schweiz. med. Wchnschr. **71**:1290, 1941. (*g*) Mach, R. S.; Babel, J., and Naville, M.: Syndromes muco-cutanés avec complications oculaires (érythème polymorphe, iritis récidivante aphtheuse), Helvet. med. acta **7**:552, 1941. (*h*) Bechgaard, P.: Case of Recurrent Aphthous Stomatitis Accompanied by Conjunctivitis and Ulcerations of Genitals and Skin, Ugesk. f. læger **102**:1019, 1940.

16. (*a*) Behcet.[1] (*b*) Franceschetti and Valerio.[7] (*c*) Jensen.[11b] (*d*) Ephraim.[12b] (*e*) Knapp.[14] (*f*) Schultheiss-Linder.[15f] (*g*) Bechgaard.[15h] (*h*) Weekers, L., and Reginster, H.: Contribution à l'étude de l'iritis récidivante à hypopion (uvéite allergique récidivante à hypopion), Bull. Soc. belge d'opht., 1938, no. 76, p. 31; (*i*) Un nouveau syndrome: Iritis, ulcéres aigus de la bouche et de la vulve: Sa parenté avec l'iritis récidivante à hypopion, Arch. d'opht. **2**:697, 1938.

17. Whitwell.[5] Curth.[6]

18. Franceschetti and Valerio.[7] Bechgaard.[15h]

19. Bechgaard.[15h] Weekers and Reginster.[16h] Popoff, L.: L'ulcere vulvaire aigu de Lipschuetz comme manifestation particulière de l'érythème polymorphe et de l'érythème noueuxe, Bull. Soc. franç. de dermat et syph. **45**:1254, 1938.

They concluded that these reactions were not specific. This observation is apparently not a common one, as other investigators do not report this type of reaction. Arthritis and rheumatic pain are not uncommon observations. All the reported cases have occurred in patients between the ages of 15 and 45, and male patients have predominated. The patients have been apparently in good health and in many instances acquired lesions without any systemic reaction, although in some the onset was marked with attacks of chills and fever. Berlin [9] is the only author who reported a death with observations at autopsy. His patient had recurrent attacks over a five year period, and one week prior to death there occurred attacks of convulsions followed by loss of consciousness. The observations at autopsy were not specific in that the patient had edema of the liver and multiple small foci of inflammation and softening of the brain. There is no specific histopathologic picture of this triple symptom complex.

REITER'S DISEASE

In 1916, Reiter [20] described a disease entity which occurred in a German soldier and consisted of urethritis, conjunctivitis and arthritis. This patient had nonspecific urethritis and severe conjunctivitis and subsequently acquired rheumatic pains and swelling of the joints. Later, purulent conjunctivitis and iritis occurred. During the course of the illness there was continued remittent fever. Examination of repeated smears of the urethral discharge failed to reveal gonococci, but Reiter stated that he was able to cultivate a spirochete from the blood, which he called Spirochaeta forans. There have been published no subsequent reports in the literature to substantiate the latter observation. Prior to World War II only two reports of this condition had appeared in the English literature. One was by Frühwald,[21] who published 2 cases which were said to be similar to the ones reported by Reiter, and 1 case was reported by Bauer and Engleman.[22] It should be emphasized that although Frühwald [21] stated that Reiter's original patient had gonorrhea, Reiter had specifically pointed out that on several examinations gonococci were not found. After Reiter's report Junghanns,[23]

20. Reiter, H.: Ueber eine bisher unbekannte Spirochäteninfektion (Spirochaetosis arthritica), Deutsche med. Wchnschr. **42**:1535, 1916.

21. Frühwald, R.: So-Called Spirochaetosis Arthritica (Reiter, 1916), Urol. & Cutan. Rev. **32**:7, 1928.

22. Bauer, W., and Engleman, E.: A Syndrome of Unknown Etiology Characterized by Urethritis, Conjunctivitis, and Arthritis (So-Called Reiter's Disease), Tr. A. Am. Physicians **57**:307, 1942.

23. Junghanns, O.: Ein weiterer Fall von Urethritis non gonorrhoria und septischer Allgemeinerkrankung, Deutsche med. Wchnschr. **44**:1304, 1918.

Michael,[24] Sommer [25] and Stühmer [26] also reported cases. Some of the subsequent reports have included patients in whom only two members of the original triad were considered as sufficient for a diagnosis of Reiter's disease. Hollander [27] and his co-workers reported 25 cases, in 14 of which there were urethritis and arthritis but not conjunctivitis. Epstein [28] reported a case in which the patient had arthritis, conjunctivitis and a keratosis blennorrhagica–like eruption. In 1944, Lever and Crawford [29] questioned how many of the 44 cases reported up to that time should be included, because in some the triad was not complete and in others the bacteriologic studies were not sufficient to exclude the presence of a gonococcic infection. These authors also suggested the possibility that keratosis blennorrhagica should be included as a symptom of Reiter's disease. Wiedemann,[30] Kuske [31] and Kruspe [32] were among those who expressed the belief that keratosis blennorrhagica may be a symptom of Reiter's disease. Reports subsequent to the original description have added new symptoms involving the skin, mucous membrane and eyes which were not originally included. In table 2 are data concerning the disease picture as it affects the various organs.

Lesions on the Genitalia.—If these cases are to fulfil the original criteria laid down by Reiter, nonspecific urethritis must be proved or a history of it must be determined. Warthin [33] reported 4 cases; 3 of these patients had cutaneous lesions on the genitalia. One patient had eight circinate ulcerations on the glans penis. The second patient also had ulcers on the prepuce, which Warthin described as balanopos-

24. Michael, M.: Beiträge zur Kasuistik und Differential-Diagnose seltener frühluetischer und gonorrhoischer Komplikationen, Dermat. Ztschr. **24**:406, 1917.

25. Sommer, A.: Drei wahrscheinlich als "Spirochaetosis arthritica" (Reiter) anzusprechende Krankheitsfälle, Deutsche med. Wchnschr. **44**:403, 1918.

26. Stühmer, A.: Ueber die sogenannte "Spirochaetosis arthritica" (Reiter), München. med. Wchnschr. **68**:769, 1921.

27. Hollander, J. L.; Fogarty, C. W.; Abrams, N. R., and Kydd, D. M.: Arthritis Resembling Reiter's Syndrome: Observations in Twenty-Five Cases, J. A. M. A. **129**:593 (Oct. 27) 1945.

28. Epstein, E.: Reiter's Disease: Comparison with Keratosis Blennorrhagica and with Psoriasis Arthropathica, Arch. Dermat. & Syph. **56**:191 (Aug.) 1947.

29. Lever, W. F., and Crawford, G. M.: Keratosis Blennorrhagica Without Gonorrhea (Reiter's Disease?), Arch. Dermat. & Syph. **49**:389 (June) 1944.

30. Wiedemann, H.: Reitersche Erkrankung, Wien. klin. Wchnschr. **47**:1245, 1934.

31. Kuske, H.: Ueber die Hauterscheinungen bei Morbus Reiter, Arch. f. Dermat. u. Syph. **179**:58, 1939.

32. Kruspe: Zur Aetiologie der Reiterschen Erkrankung, Dermat. Wchnschr. **112**:457, 1941.

33. Warthin, T. A.: Reiter's Syndrome, Am. J. Med. **4**:827, 1948.

thitis. His third patient had inflammation of the urethral meatus. Beck,[34] Postma[35] and Bauer and Engleman[22] described an eruption on the penis which they called balanitis circinata.

Ocular Lesions.—The subject of Reiter's original paper had purulent conjunctivitis, and the vast majority of patients described in subsequent reports had similar lesions, but keratitis, iritis, episcleritis, keratitis with ulcers and macula of the cornea have also been reported by various authors.

TABLE 2.—*Reiter's Disease*

Original criteria for diagnosis
1. Urethritis, nonspecific
2. Conjunctivitis, followed by iritis
3. Rheumatic pain and swelling of joints
Symptoms added in subsequent reports
Ocular signs
1. Purulent conjunctivitis
2. Keratitis
3. Iritis
4. Episcleritis
5. Corneal ulcers
6. Maculas of the cornea
Genital lesions
1. Circinate ulcerations (balanitis circinata)
2. Balanoposthitis
3. Inflammation of the urethral meatus
Oral lesions
1. Superficial ulcers with bloody crusts
2. Canker sores in the mouth
Cutaneous lesions
1. Urticaria
2. Erythema simplex
3. Erythema nodosum
4. Erythema multiforme
5. Keratosis blennorrhagica
6. Pustules
Joint signs
1. Rheumatoid arthritis

Joint Signs.—The joint signs reported have varied from simple arthralgia to well defined rheumatoid arthritis. Lever and Crawford[29] stated that the arthritis observed in the condition known as Reiter's disease resembles gonorrheal arthritis in many respects. Occasionally

34. Beck, F.: Ein Beitrag zur der sog. Spirochaetosis arthritica Reiter, Med. Klin. **33**:1162, 1937.

35. Postma, C.: A Case of Reiter's Disease, Acta dermat.-venereol. **18**:691, 1937.

a single joint is involved, although in the majority of the cases the involvement is polyarticular. Permanent damage to the joints has not been reported.

Oral Lesions.—Warthin [33] is the only author who has reported oral lesions. One of his patients had superficial ulcerations with bloody crusts on the lip and on the adjacent buccal membranes, and another of his patients had severe canker sores in his mouth for four days prior to reporting for examination and treatment.

Cutaneous Lesions.—Epstein [28] stated that cutaneous manifestations were usually absent, but that nonspecific eruptions such as urticaria, simple erythema, erythema nodosum and erythema multiforme were sometimes seen. Several authors have reported the presence of keratosis blennorrhagica, pustules, balanitis, perimeatal ulcerations and balanitis circinata.

Etiology.—As previously stated, Reiter described a spirochetemia, but subsequent reports have failed to verify this observation. Lever and Crawford [29] stated that only those cases which have all three of the basic manifestations should be included in this classification, and, as Epstein [28] pointed out, this attitude is justified until a causative organism or a specific diagnostic test for Reiter's disease is discovered. Manson-Bahr [36] stated the belief that the disease is the "familiar dysenteric polyarthritis." Several physicians [37] in recent reports indicated the possibility that this syndrome represents late sequelae of a bacillary (Shiga or Flexner) dysentery. Some expressed the opinion that it is a virus disease. Pastinszky [38] stated the belief that the syndrome must be considered as a specific allergic or para-allergic reaction following an intestinal bacillary infection in which the reacting organs are the urethra, the bladder, the conjunctiva and the joints, with eventual involvement of other organs. The most recent work on the etiology of this syndrome is that of Warthin,[33] who was able to culture pleuropneumonia-like organisms from the urine and the effusion fluid of the knee.

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36. Beiglböck, W.: Zur Behandlung der Reiterschen Krankheit (Ruhrrheumatismus), Deutsche. med. Wchnschr. **69**:803, 1943; abstracted by Manson-Bahr, Bull. War Med. **4**:653, 1944.

37. Herson, R. N.: Reiter's Disease, Brit. M. J. **2**:275, 1946. Marsh, F.: Reiter's Disease, ibid. **2**:275, 1946. Wood, P.: Reiter's Disease, Brit. M. J. **2**:309, 1946. Kersley, G. D.: Reiter's Disease, ibid. **2**:309, 1946. Baxter, C. R.: Reiter's Disease, Brit. M. J. **2**:858, 1946. Forbes, D.: A Case of Reiter's Disease, Brit. M. J. **2**:859, 1946.

38. Pastinszky, E.: Investigations on Etiology of Reiter's Disease or the Conjunctival-Urethral-Synovial Syndrome, Acta dermat.-venereol. **27**:415, 1947.

STEVENS-JOHNSON DISEASE

In 1922, Stevens and Johnson [39] reported a "new syndrome" in which they had found a generalized cutaneous eruption, stomatitis and conjunctivitis. They made the claim that their cases were unlike anything previously described and chose to coin the phrase "eruptive fever associated with stomatitis and ophthalmia." Since this original report, other authors [40] applied the term Stevens-Johnson syndrome to eruptive fevers which they considered similar to the first cases. Two cases were described originally by Stevens and Johnson, both of which occurred in young boys aged 7 and 8 and were classed among the group of infectious, eruptive fevers; however, it was stressed that there was nothing to indicate that the illness was spread by immediate contagion. The first patient had been quite ill with a septicemia due to Staphylococcus aureus two and one half months prior to the onset of this illness. He first acquired a sore throat and general malaise which was followed by purulent conjunctivitis and a reddish maculopapular eruption on the trunk. The lips, tongue and buccal mucosa were edematous and covered with blood crusts, bullae and superficial ulcerations. The cutaneous lesions were described as "discrete, oval, brownish and purple papular lesions," several of which presented central necrosis.

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39. Stevens, A. M., and Johnson, C. F.: A New Eruptive Fever Associated with Stomatitis and Ophthalmia, Am. J. Dis. Child. **24**:526 (Dec.) 1922.

40. (*a*) Kove, S.: Stevens-Johnson Syndrome (Eruptive Fever with Stomatitis and Conjunctivitis), Am. J. M. Sc. **210**:611, 1945. (*b*) Wentz, H. S., and Seiple, H. H.: Stevens-Johnson Syndrome: Variation of Erythema Multiforme Exudativum (Hebra); Report of Two Cases, Ann. Int. Med. **26**:277, 1947. (*c*) Ginandes, G. J.: Eruptive Fever with Stomatitis and Ophthalmia: Atypical Erythema Exudativum Multiforme (Stevens-Johnson), Am. J. Dis. Child. **49**:1148 (May) 1935. (*d*) Murphy, R. C., Jr.: Eruptive Fever Involving the Mouth and Eyes (Stevens-Johnson Disease): Report of Case, New England J. Med. **230**:69, 1944. (*e*) Ageloff, H.: Erythema Multiforme Bullosum with Involvement of the Mucous Membranes of the Eye and Mouth (Stevens-Johnson Disease), New England J. Med. **223**:217, 1940. (*f*) Givner, J., and Ageloff, H.: Stevens-Johnson Disease with Complete Visual Recovery, New York State J. Med. **41**:1762, 1941. (*g*) Erger, B. D.: Erythema Multiforme Pluriorificialis (Stevens-Johnson Disease), Mil. Surgeon **95**:308, 1944. (*h*) Goldfarb, A. A.: A Case of Stevens-Johnson Disease (Erythema Multiforme Bullosa) Treated with Penicillin, J. Pediat. **28**: 579, 1946. (*i*) Wright, D. O.; Gold, E. M., and Jennings, G.: Stevens-Johnson Syndrome: Report of Nine Patients Treated with Sulfonamide Drug or Penicillin, Arch. Int. Med. **79**:510 (May) 1947. (*j*) Gilbert, T. M., and Hing, S. R.: The Stevens-Johnson Syndrome, M. J. Australia **2**:774, 1946. (*k*) Nellen, M.: Stevens-Johnson Syndrome, Lancet **1**:326, 1947. (*l*) Murray, J. O.: Stevens-Johnson Syndrome, ibid. **1**:328, 1947. (*m*) Patz, A.: An Eruptive Fever Involving Skin and Mucous Membranes (Stevens-Johnson Disease), New England J. Med. **236**:697, 1947. (*n*) Richards, J. M., and Romaine, H. H.: Keratoconjunctivitis Sicca, Am. J. Ophth. **29**:1121, 1946. (*o*) Umiker, W., and Grofoot, M.: Stevens and Johnson's Disease, U. S. Nav. M. Bull. **46**:1466, 1946.

Other physical findings included splenomegaly, hepatomegaly and a systolic mitral murmur. In the second case they reported, the condition was somewhat similar but severer, since corneal ulceration followed the purulent conjunctivitis and resulted in complete destruction of the globe. The cutaneous lesions became hemorrhagic, and this patient had concomitant pneumonia of the lobular type. Both patients recovered, the only residual finding being the ocular destruction in the second case. In the past twenty-six years there have been numerous reports in the literature recorded as of Stevens-Johnson disease, but the description is still limited chiefly to the clinical features. The illness usually attacks males in the first three decades; however, exceptions to this tendency are not uncommon. Jones,[41] Richards [40n] and Ageloff [40e] described this symptom complex in female patients. Jones's patient was an Irish woman 56 years of age. Apparently, this syndrome is commoner in the United States than elsewhere and Caucasians are more commonly affected.

In table 3 are data concerning the disease picture as it affects the various organs.

Ocular Lesions.—Ocular manifestations vary from mild conjunctivitis to purulent conjunctivitis, corneal ulceration and panophthalmitis with destruction of the globe.[39] Ginandes,[40c] reviewing part of the available literature on the subject, reported 9 cases, in 7 of which the patient eventually became blind after pyococcal involvement of the ocular tissues. Erger [40g] and Kove [40a] claimed specificity of this clinical entity on the basis of severe ocular involvement, a feature which is not usually stressed in discussions of other members of the erythema multiforme group. Keil,[42] however, expressed the belief that the name Stevens-Johnson disease has been applied to these cases of erythema multiforme exudativum with severe ocular involvement. The latter concept is shared by Soll,[43] Klauder [44] and Goldfarb.[40h] Corneal and conjunctival scarring with the formation of keratoconjunctivitis sicca has been listed also as an ocular complication.[40n] Givner and Ageloff [40f] expressed the feeling that the almost uniform occurrence of Staph. aureus in these cases is of some definite significance.

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41. Jones, W. Y.; Talbot, F., and King, W. F.: Stevens-Johnson disease, Am. J. Ophth. **29**:185, 1946.

42. Keil, H.: Erythema Multiforme Exudativum (Hebra): Clinical Entity Associated with Systemic Features, Ann. Int. Med. **14**:449, 1940.

43. Soll, E. N.: Eruptive Fever with Involvement of the Respiratory Tract, Conjunctivitis, Stomatitis and Balanitis, Arch. Int. Med. **79**:475 (May) 1947.

44. Klauder, J. V.: Ectodermosis Erosiva Pluriorificialis: Its Resemblance to Human Form of Foot and Mouth Disease and Its Relation to Erythema Exsudativum Multiforme, Arch. Dermat. & Syph. **36**:1067 (Nov.) 1937.

Cutaneous Lesions.—Stevens and Johnson described a maculopapular eruption of a brownish color. Some of the lesions became hemorrhagic; some showed central necrosis, and some were covered by a horny scale. The majority of patients in subsequent reports have had generalized eruptions chiefly of a vesicular or bullous nature. In a few of the cases included in this category there have not been cutaneous lesions.[45]

Oral Lesions.—The oral lesions have been primarily of a vesicular or bullous type, with ulceration, blood crusting and fissuring. Edema

TABLE 3.—*Stevens-Johnson Disease*

Original criteria for diagnosis
1. Generalized maculopapular eruption
2. Purulent conjunctivitis with corneal ulceration
3. Ulceromembranous stomatitis
4. Fever
Symptoms added in subsequent reports
Ocular signs
1. Mild conjunctivitis
2. Panophthalmitis with destruction of bulb
3. Keratoconjunctivitis sicca
Genital lesions
1. Nonspecific urethritis
2. Balanitis
3. Vaginal ulcers
Oral lesions
1. Vesiculobullous eruption
2. Pseudomembranous formation
3. Extensive ulceration of the pharynx
Cutaneous lesions
1. Vesicular or bullous eruption
2. No skin lesions
3. Erythema multiforme lesions
Joint signs
1. None reported
Miscellaneous
1. Afebrile course
2. Esophageal ulceration and hematemesis
3. Tracheobronchial ulceration
4. Pneumonia

of the affected parts has been reported as an outstanding feature, and formation of pseudomembranes is presumably typical. Extensive ulceration of the pharynx has also been reported,[40g] with dysphagia and excess salivation as accompanying features.

Genital Lesions.—Involvement of other mucosal surfaces has been featured more prominently in the later literature. Periurethral and

45. Soll.[43] Gilbert and Hing.[40j]

urethral lesions have been described. Balanitis, nonspecific urethritis and vaginal lesions have been mentioned.[40e]

Miscellaneous.—Pneumonia has been mentioned as a common complication or an integral part of the illness.[46] Tracheobronchial and pulmonary complications are frequently observed. The most striking feature of the illness is the severity of the constitutional reaction. The onset usually occurs with fever and general malaise, although normal temperatures have been reported.[40l] Patients soon become prostrated with signs of overwhelming toxicity. The fever may last for four to thirty days, and nausea and vomiting may accompany the discomfort. Hematemesis has been reported as occurring, presumably from esophageal ulceration. Kove [40a] and Murphy [40d] both stressed the constant nature of the enanthem rather than the exanthem. Recovery is rarely rapid, and relapses are an outstanding feature of the disease.

Etiology.—Laboratory and other special studies are rarely of a specific nature. Results of the studies of the blood are usually within relatively normal limits although leukopenia has been mentioned by some investigators [47] and mild leukocytosis by others. The bacteriologic studies for the most part have revealed mixed infections, chiefly pyococcal, and it has been assumed that these represent secondary invaders. In a large percentage of cases, however, Staph. aureus has been grown from the infected areas and occasionally in pure culture. There has been a striking paucity of Vincent's organisms in the buccal cavities of these patients. A specific etiologic agent has not as yet been discovered. Edgar and Syverton [48] suggested a virus etiology and attempted to produce lesions by animal inoculation with fluid from vesicles but without success. Subsequent passage to other animals was also without results. Givner and Ageloff [40f] were unable to demonstrate elementary bodies on smears. Cultures of material from conjunctival lesions grown on chorioallantoic membrane of the chick yielded no pathogens. In a further attempt to establish a virus as the etiologic factor, detailed studies were carried out by Soll.[43] Since it is difficult to obtain vesicle fluid from oral lesions, saliva was used, but efforts to produce a growth on chorioallantoic membranes were not very successful. Lesions were produced, but the responsible agent was not identified.

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46. Fletcher, M. W. C., and Harris, R. C.: Erythema Exudativum Multiforme (Hebra) — Bullous Type: Cases Seen in Contagious Disease Hospital, J. Pediat. **27**:465, 1945. Erger.[40g] Soll.[43] Gilbert and Hing.[40j] Nellen.[40k] Murray.[40l]

47. Stevens and Johnson.[39] Ageloff.[40e] Patz.[40m]

48. Edgar, K. J., and Syverton, J. T.: Erythema Exudativum Multiforme with Ophthalmia and Stomatitis, J. Pediat. **12**:151, 1938.

ECTODERMOSIS EROSIVA PLURIORIFICIALIS

Rendu [49] and Fiessinger, Wolff and Thévenard [50] described a syndrome involving the mucous membranes of the mouth, conjunctiva and genitalia, with a vesicular eruption on the extremities. In 1923 the term "ectodermose érosive pluriorificielle" was used. Since that time Jausion and Diot, Aubert, de Lavergne, Chantegreil and Kumer have described similar cases under this title (cited by Klauder [44]). Klauder [44] was the first to report cases of this type in the American literature. Since that time few have labeled the disease ectodermosis erosiva pluriorificialis. This symptom complex is usually acute in onset with the constitutional prodromes of malaise, headache and chills. The patients invariably have temperatures ranging from 100 to 104 F. and complain of sore throat. When the picture is fully developed there is vesiculation of the buccal mucosa which eventually leads to ulceration. Lesions also occur on the lips and tongue; extensive severe stomatitis may develop; pseudomembrane formation is common, and the pharyngeal mucosa and tonsils are frequently involved. Conjunctivitis usually is not severe, but a seropurulent discharge may develop. Occasionally there is rhinitis with ulceration of the nasal mucosa. Vesiculation of the urethral meatus, vagina and anus has been described. Klauder [44] stressed the fact that the vesicular cutaneous eruption is usually located on the hands and feet and that differentiation from the human form of foot and mouth disease by guinea pig inoculation is essential. Other authors have described papular, macular and vesiculopapular eruptions with hemorrhagic skin lesions typical of erythema multiforme exudativum. Involvement of the conjunctiva and buccal mucosa has been reported in the absence of cutaneous manifestations. Laboratory studies in these cases have not led to any specific etiologic factor. Klauder [44] reported 4 cases and concluded that this syndrome represents a variant of erythema multiforme.

In table 4 are data concerning the disease picture as it affects various organs.

Cutaneous Lesions.—Cutaneous manifestations, as described in the earlier reports,[51] were limited to a vesicular eruption principally involving the hands and feet. Since then, however, in other reports there have been described macular and papular eruptions with the eventual development and predominance of vesicular and bullous lesions. Cases have been described in which the cutaneous manifestations were absent.[50]

49. Rendu, R.: Sur un syndrome caracterisé par l'inflammation simultanée des toutes les mugueuses externes (conjunctivale, nasale, linguale, bucco-pharyngée, avale et balono-préputiale) coexistant avec une éruption varicelliforme puis purpurique des quatre membres, Rev. gén. de clin. et de thérap. **30**:351, 1916.

50. Fiessinger, N.; Wolff, M., and Thévenard, A.: Ectodermose érosive pluri-orificielle. Bull. et mém. Soc. méd. d. hôp. de. Paris **47**:446, 1923.

51. Rendu.[49] Fiessinger, Wolff and Thévenard.[50]

Oral Lesions.—Lesions of oral and other mucous membranes are almost always of the vesicular or bullous type with or without subsequent ulceration. There may be extensive erosion of the gums, tongue, buccal mucosa and pharynx, with severe edema and difficulty in swallowing and breathing. It was because of the pronounced buccal involvement that Fiessinger and Rendu stated the opinion that they were dealing with a new clinical entity. Klauder [44] expressed the belief that the term "ectodermosis erosiva pluriorificialis" should be applied to those cases of erythema multiforme with severe involvement of oral and other mucous membranes.

TABLE 4.—*Ectodermosis Erosiva Pluriorificialis*

Original criteria for diagnosis
1. Severe ulcerative stomatitis
2. Conjunctivitis, mild
3. Varicelliform eruption with purpura on the extremities
4. Balanitis
Symptoms added in subsequent reports
Ocular signs
1. Seropurulent conjunctivitis
2. Conjunctival vesiculation
3. Keratitis and cicatrization
Genital lesions
1. Ulceration of the vagina
2. Urethritis, nonspecific
Oral lesions
1. Vesiculobullous type of eruption, with or without ulceration
2. Extensive ulceration of the pharynx
Cutaneous lesions
1. Macular eruption
2. Papular eruption
3. Generalized vesicular or bullous eruption
4. Iris lesions of the palms and soles
Joint signs
1. Transient arthritis
Miscellaneous
1. Tracheobronchial ulceration
2. Pneumonitis

Genital Lesions.—Schreuder [52] reported ulceration of the vaginal mucosa. Urethritis with balanitis has been described by Klauder,[44] Silver,[53] Lever [54] and others.

52. Schreuder, J. J. C.: Pluri-Orificial Erosive Ectodermosis in Woman, Nederl. tijdschr. v. geneesk. **1**:874, 1926.

53. Silver, N.: Ectodermosis Erosiva Pluriorificialis (Klauder's Syndrome), Ann. Int. Med. **24**:499, 1946.

54. Lever, W. F.: Severe Erythema Multiforme: Report of Two Cases of Type Ectodermosis Erosiva Pluriorificialis, with Development of Cicatricial Conjunctivitis and Keratitis in One Case, Arch. Dermat. & Syph. **49**:47 (Jan.) 1944.

Ocular Lesions.—Conjunctivitis, although invariably present, usually does not assume the proportions described by Stevens and Johnson [39] in their report. It is usually limited to superficial injection of conjunctival vessels with a serous or seropurulent discharge, and in an occasional patient conjunctival vesiculation develops. Lever [54] reported cicatrization and keratitis in 1 case which he chose to call "ectodermosis erosiva pluriorificialis."

Joint Signs.—Arthritis is not an outstanding feature of this disease, but when it does occur it is usually transient and is associated with the onset of the illness. Permanent joint changes have not been described.

Etiology.—Laboratory studies have been of little or no avail in determination of the etiology of this syndrome. Cultural studies reveal common or mixed organisms grown from the involved surfaces. There is no specific laboratory picture.

COMMENT ON CASES

In table 5 an attempt is made to present the essential observations in 11 cases of mucocutaneous-ocular syndromes. Statistical data drawn from such a small series are probably of minor importance; however, it may be stated that in our series there has been no racial or sex predominance. Nine of the patients were under 35 years of age.

Although the severity of the tissue reaction has varied, it may be stated that the basic process in all these cases was similar. The mucosal lesion appeared to be one of initial vesiculation with subsequent ulceration. In the majority of cases, there was secondary invasion by organisms normally found in that particular area. Ocular complications were presumably related to secondary infection. Corneal ulceration, uveal tract disease and scarring always followed initial catarrhal conjunctivitis. Four of these patients had no urogenital symptoms; 2 complained of dysuria, 4 had nonspecific urethritis and 2 had balanitis without a discharge.

Cutaneous lesions were, for the most part, of the erythema multiforme type with frequent iris and annular configuration. Vesiculobullous lesions were seen in 7 cases. Keratosis blennorrhagica was seen in the case with severe joint signs.

The commonest complications were nasopharyngitis, tracheobronchitis and pneumonia. Specific organisms were not isolated in the cases in which there were pulmonary lesions. In all these patients the temperature was elevated. The febrile course lasted from three to thirty-five days. Relapses with fever and exacerbation of lesions occurred in several cases. In 1 of our cases there were recurring attacks for fourteen years. There was one fatality (case 3).

TABLE 5.—*Data Concerning Eleven Cases of Mucocutaneous-Ocular Syndromes*

Case No.	Sex, Age, Race of Patient	Oral Lesions	Ocular Lesions	Joint Lesions	Urogenital Lesions	Cutaneous Lesions	Temperature	Concomitant Pathologic Changes	Laboratory Observations
1	F, 18, W	Ulcerative lesions of buccal mucosa, gums and tongue	Mild conjunctivitis with granuloma formation	None	Dysuria only	Generalized bullous eruption; few well defined maculopapules	98.6-101 F., 27 days	Pharyngitis; transient alopecia and onycholysis	Hb., 12.6-14.0 Gm.; RBC, 4.3-6.0; WBC, 4,850-10,000 (eosinophils, 0-10%); urinalyses, negative; sedimentation rate, 0 mm.; heterophil antibodies test, negative; cold agglutinin test, negative; cultures, Staph. aureus
2	M, 37, W	Gingival, buccal and pharyngeal ulceration	Purulent conjunctivitis; minimal corneal ulceration	Arthritis, destructive	Balanitis with purulent urethritis	Keratosis blenorrhagica type of eruption	98.6-102 F., 35 days	Onycholysis	Hb., 9.6-14.0 Gm.; WBC, 2,000-10,850; sedimentation rate, 29 mm.; cultures, no gonococci; normal flora; virus studies not done
3	M, 65, N	Severe stomatitis with ulceration and pronounced edema	Severe purulent conjunctivitis	None	Few superficial penile ulcers; no discharge	Generalized maculopapulous eruption with iris and annular lesions; no bullae	103-106 F., 2 days; fatal	Pneumonitis, left lower lobe; arteriosclerotic heart disease with moderate enlargement	Hb., 16.1 Gm.; RBC, 4.7 Gm.; WBC, 10,450, with normal differential count; urine, 3+ albumin; culture, Staph. aureus
4	M, 10, N	Superficial ulceration of lips and buccal mucosa	Severe purulent conjunctivitis	None	None	Generalized vesicular eruption; ulceration and pustule formation; few maculopapules on extremities	98-103 F., 9 days	Pneumonitis, base of right lung; nasopharyngitis severe; neurofibroma of the left orbit	Hb., 84-88%; WBC, 5,400-6,800; urine, 1-4+ albumin; culture, normal flora; cold agglutinin test, negative
5	F, 32, W	None	Mild conjunctivitis	Transient arthritis	None	Generalized maculopapular eruption; bullae on extremities	100-101.8 F., 3 days	None	Hb., 12.0-13.6 Gm.; WBC, 12,000-24,000; urinalyses, negative; vesicle fluid cultures, sterile; other cultures, Staph. aureus; virus studies not done
6	M, 25, N	Bullous lesions on lips and buccal mucosa with ulceration and crusting	Mild to purulent conjunctivitis with uveitis and slight corneal scarring	None	Purulent urethral discharge without lesions	Iris and annular pinkish maculopapules; scattered vesicles; few pigmented lesions; relapses for fourteen years	99-101 F., intermittent	Rectal bleeding	Urinalyses, WBC only; CBC, normal; platelets, 178,000; Rumpel-Leede test, positive; cultures and serologic studies not done

Case No.	Sex, Age, Race of Patient	Oral Lesions	Ocular Lesions	Joint Lesions	Urogenital Lesions	Cutaneous Lesions	Temperature	Concomitant Pathologic Changes	Laboratory Observations
7	M, 23, W	Bullae of lips with fissuring and crusting; superficial ulceration of tongue and buccal surface; white gingival plaques with hypertrophic papillae	Marked conjunctivitis with purulent discharge and corneal infiltration (photophobia severe)	Swelling and tenderness of both ankles (see fluid culture)	Severe purulent discharge with corneal and shaft lesions of macular type	Bullous eruption with scattered well defined macules on extremities and trunk	Febrile course	Decided weight loss; progressive downhill course and anuria (cystotomy performed); pronounced dysphagia with pharyngitis	Urethral cultures negative for gonococci; joint fluid, sterile; urinalyses, WBC only; sedimentation rate, 0 mm.; roentgenogram of joints, rheumatoid pattern seen
8	F, 15, N	Decided edema of lips with buccal ulcers and gingivitis; hyperplastic gingiva	Blepharitis and purulent conjunctivitis; corneal ulcer; recurrent mild conjunctivitis	Severe arthralgia with swelling and tenderness (ankles and interphalangeal joints)	Superficial vaginal ulcers with purulent discharge (no gonococci)	None at onset; later mild macular erythema multiforme, generalized	98-100 F., intermittent	Rheumatic diathesis (possible); minute ulceration of rectal mucosa; hepatomegaly minimal	Blood picture, normal; urinalyses, negative; sedimentation rate, elevated; serologic test for syphilis, negative; agglutination test, negative; roentgenograms of chest, skull, long bones—normal
9	F, 32, W	None	Mild conjunctivitis with purulent exudate	Monarticular arthralgia; no joint changes	None	Maculopapular erythema multiforme with bullae on upper extremities	99-102 F., 6-8 days	Pharyngitis and tracheobronchitis; no pulmonary signs; roentgenogram of chest normal	Blood picture—leukocyte count, 12,000-30,000, with predominance of polymorphonuclear cells; urinalyses, normal; blood culture, sterile; bulla fluid culture, sterile; culture from throat, Staph. aureus; serologic test for syphilis, negative
10	M, 7, N	Pronounced edema of lips with fissures; superficial ulceration of the buccal mucosa with blood crusting	Pronounced purulent conjunctivitis, bilateral, with severe edema; cornea normal	None	Mild dysuria, no distinct lesions noted; no urethral discharge	Maculopapular erythema multiforme with iris and annular lesions, generalized; no bullae	99-104 F., 12 days	Nasal ulceration with severe pharyngitis	Blood picture—WBC, 6,000-20,000, with predominance of polymorphonuclear cells; serologic test for syphilis, negative; blood culture, sterile; culture from eye, Staph. albus; agglutination test, negative; sedimentation rate, 26 mm.
11	F, 5, W	Bullae on lips with crusting and fissuring; buccal mucosa normal	Mild purulent conjunctivitis	None	None	Maculopapular erythema multiforme with scattered bullae	99-100.4 F., 10 days	Severe follicular tonsillitis; minimal pneumonitis, right lung	Blood picture—WBC, 8,000-14,000 with normal differential count; urinalyses, normal; tuberculin test, negative; spinal fluid, normal; culture from throat, green-producing streptococcus, Staph. albus (hemolytic); roentgenogram of chest, pneumonitis

Laboratory studies were of little value in establishment of a diagnosis. Leukocyte counts were usually normal or slightly elevated, and urinalyses revealed only transient albuminuria. Cultures produced mixed growths except in those instances in which pure cultures of staphylococci were obtained. It should be noted that, except for heterophil antibody and cold agglutinin titrations, virus studies were not performed.

From the data made available by these case studies, we were unable to differentiate these syndromes from the clinical or laboratory standpoint. It is our belief that (with the possible exception of case 2) they represented variants of erythema multiforme exudativum.

COMMENT

A survey of the literature impressed us that these syndromes are variants of erythema multiforme, the only possible exception being that symptom complex known as Reiter's disease. Because of indiscriminate efforts to extend the scope of this syndrome with the addition of new manifestations by succeeding authors the result in its present day picture is a confused mass of symptoms which resemble erythema multiforme exudativum. The confusion is not lessened by the statement [27] that atypical cases may exist in which only two of the three symptoms need be present. Epstein [28] stated that "non-specific eruptions such as simple erythema, urticaria, erythema nodosum, and erythema multiforme may occur but are not of diagnostic significance." Earlier statements in the present article point out that several authors expressed the belief that keratosis blennorrhagica is a part of the picture of Reiter's disease; however, Ladany and Hughes [55] stated that erythema, urticaria and erythema multiforme–like or erythema nodosum–like, as well as hemorrhagic-bullous, lesions are to be considered as different evolutionary stages of keratosis blennorrhagica. The conflicting occurrence of symptoms in the published case reports and the statements of these authors demonstrate that the existence of Reiter's disease as an entity has not been proved beyond doubt.

A review of the published data on the so-called Stevens-Johnson disease reveals that that condition is indeed a vague entity. We agree with Bradlow and Schless [56] that "The differences in the material described are quite extreme and the criteria laid down by the various authors for its diagnosis are . . . conflicting." These authors stated the belief that the term Stevens-Johnson disease is synonymous with

55. Ladany, E., and Hughes, J. D.: Etiologic Considerations of Keratosis Blennorrhagica: Report of Case in Which Penicillin Was Used, Arch. Dermat. & Syph. **54**:150 (Aug.) 1946.

56. Bradlow, P. A., and Schless, R. A.: An Unusual Eruptive Fever Involving the Skin and Mucous Membranes, J. Pediat. **32**:293, 1948.

erythema multiforme exudativum. In the earlier part of this thesis it was pointed out that a number of authors expressed the opinion that this is a serious type of erythema multiforme exudativum. Claims that ectodermosis erosiva pluriorificialis is a specific entity are limited to the French literature. Klauder [44] was the first in this country to report cases, and he concluded that the condition is a severe type of erythema multiforme.

The so-called triple symptom complex of Behcet has no specific clinical picture, and a careful analysis of the reported cases reveals a striking similarity to the other symptom groups. There have been many contributions to aid in increasing the confusion, and notable among these has been the statement that it is unnecessary for all three members of the triad to be present in order for the diagnosis of Behcet's disease to be established.[6] The fact that iritis with hypopyon is the most commonly reported ocular lesion has led to the belief that it is the outstanding finding in this syndrome and that in order for one to make a diagnosis of Behcet's disease this lesion must be present; however, in none of the original cases was the patient so affected. Löffler, Martin and Babel [57] considered erythema multiforme exudativum, ectodermosis erosiva pluriorificialis, Stevens-Johnson disease, Behcet's disease and Baader's dermatostomatitis as the same entity. They reported 30 cases of severe erythema multiforme and stated that swollen and painful joints occur in 20 per cent. We agree with their statement and add Reiter's disease to this list because we believe that in its present day status it is not possible for one to distinguish it from the other members of the erythema multiforme group. Martin, Babel and Löffler [58] reported a case of bilateral relapsing conjunctivitis, corneal ulcers and iritis in a 49 year old woman with erythema multiforme. It is interesting to note that Behcet in his original report stated that a differential diagnosis between the triple symptom complex and erythema multiforme would be difficult but for reasons not too clearly defined expressed the belief that they were different. The apparent relation between these syndromes is further demonstrated when the array of symptoms which occur in the various symptoms is charted and compared.

A table of the occurrence of the ocular lesions (table 6) in the various so-called diseases shows that conjunctivitis, mild and purulent, may occur in all four groups under discussion. Keratitis, corneal ulceration, macula of the cornea and phlyctenules represent varying degrees of the same process, and the diagnostic term which is applied depends on the manifestation present at the time of the author's examination.

57. Löffler, H.; Martin, E., and Babel, J.: Zur Symptomatologie des Erythema exsudativum multiforme, Helvet. med. acta **14**:526, 1947.

58. Martin, E.; Babel, J., and Löffler, H.: Erythema polymorphe et complications oculaires, Praxis **36**:186, 1947.

The same statement may be made as regards iritis, uveitis and iritis with hypopyon. Conjunctival vesiculation, neuroretinitis hemorrhagica and symblepharon are rare findings, and only one reference to each of them is found in the literature.

TABLE 6.—*Comparative Occurrence of Ocular Lesions Reported in Four Syndromes*

	Ectodermosis Erosiva Pluri-orificialis	Stevens-Johnson Disease	Behcet's Disease	Reiter's Disease
Conjunctivitis, mild	X	X	X	X
Conjunctivitis, purulent	X	X	X	X
Keratitis	X	..	X	X
Corneal ulceration	..	X	X	X
Iritis	..	..	X	X
Iritis with hypopyon	..	..	X	..
Panophthalmitis	..	X	X	..
Episcleritis	..	..	X	X
Keratoconjunctivitis sicca	..	X	..	..
Conjunctival vesiculation	X	..	..	..
Macula of the cornea	..	..	..	X
Retinitis	..	..	X	..
Uveitis	..	..	X	..
Retinitis and choroiditis	..	..	X	..
Iridocyclitis	..	..	X	..
Phlyctenules	..	..	X	..
Symblepharon	..	..	X	..
Neuroretinitis hemorrhagica	..	..	X	..

TABLE 7.—*Comparative Occurrence of Cutaneous Lesions Reported in Four Syndromes*

	Ectodermosis Erosiva Pluri-orificialis	Stevens-Johnson Disease	Behcet's Disease	Reiter's Disease
Urticaria	..	..	..	X
Erythema simplex	..	..	..	X
Erythema multiforme	X	X	X	X
Erythema nodosum	..	..	X	X
Keratosis blennorrhagica	..	..	..	X
Pustules	..	..	X	X
Papular eruption (type not designated)	X	X	..	..
Macular eruption (type not designated)	X	X	..	..
Generalized vesicular or bullous eruption	X	X	..	..
Varicelliform eruption with purpura	X	..	..	..
Pyoderma	..	..	X	..
Seborrheic eczema	..	..	X	..
Hyperreactivity to skin tests	..	..	X	..
No cutaneous lesions	..	X	..	..

A table of the occurrence of cutaneous lesions (table 7) in the four syndromes reveals that lesions typical of erythema multiforme may be found in any of the symptom complexes but that erythema nodosum has been reported only in Reiter's disease and Behcet's disease. Case

reports have been published in which the statement is made that the patient has "a papular eruption," "a macular eruption" or "a generalized vesicular or bullous eruption," without any attempt being made to describe the individual lesions and classify them under the heading of one or another disease. It is quite possible that the occurrence of pustules, pyoderma and seborrheic eczema in patients is incidental and has no relation to the primary disease. It is difficult to understand how

TABLE 8.—*Comparative Occurrence of Oral Lesions Reported in Four Syndromes*

	Vesiculo-bullous Eruption	Pseudo-membrane Formation	Extensive Ulceration of Pharynx	Ulcers on Lips and Tongue	Canker Sores in Mouth	Ulcerative Stomatitis
Reiter's disease	..	..	..	..	X	X
Behcet's disease	..	..	..	X	..	X
Stevens-Johnson disease	X	X	X	..	..	X
Ectodermosis erosiva pluriorificialis	X	..	X	..	..	X

TABLE 9.—*Comparative Occurrence of Joint Signs Reported in Four Syndromes*

	Rheumatoid Arthritis	Arthralgia
Reiter's disease	X	X
Behcet's disease	X	X
Stevens-Johnson disease	..	..
Ectodermosis erosiva pluriorificialis	X	X

TABLE 10.—*Comparative Occurrence of Genital Lesions Reported in Four Syndromes*

	Balanitis	Vaginal Ulcers, Penile Ulcers	Non-specific Urethritis	Herpes-like Vesicles	Balanitis Circinata
Reiter's disease	X	X	X	..	X
Behcet's disease	..	X	..	X	..
Stevens-Johnson disease	X	X	X	..	..
Ectodermosis erosiva pluriorificialis	X	X	X	..	..

a diagnosis of Stevens-Johnson disease could be made in the absence of cutaneous lesions, particularly when the disease is described as "eruptive fever with ophthalmia."

The comparative occurrence of oral lesions (table 8) reveals that ulcerative stomatitis has been reported in all four syndromes. Vesiculo-bullous eruptions, ulcers of the lips and tongue and ulceration of the pharynx probably represent different stages of the same process. Canker sores are nonspecific and could represent any eroded or ulcerative lesion in the oral cavity.

Joint signs (table 9) are not reported in those cases of the so-called Stevens-Johnson disease reviewed in this article. Rheumatoid arthritis and arthralgia are the outstanding symptoms in those cases reported as Reiter's disease, but they have also been reported as occurring in the other two syndromes as well.

An analysis of the occurrence of the genital lesion (table 10) reveals the common occurrence of vaginal or penile ulcers in all four of the syndromes; however, urethritis and balanitis have not been described in those cases reported as Behcet's disease which have been reviewed in this report.

CONCLUSIONS

1. A review of the literature on Behcet's disease, Reiter's disease, Stevens-Johnson disease and ectodermosis erosiva pluriorificialis has been presented together with 11 case reports.

2. According to the present day concept, all these so-called entities differ decidedly from the descriptions in the original report. These changes are primarily due to indiscriminate efforts to extend the scope of these syndromes.

3. The present status of these syndromes reveals so many points of pronounced similarity that the conclusion is reached that they are all probably variants of erythema multiforme exudativum. The only possible exception to this statement is so-called Reiter's disease.

4. Until the specific etiology is discovered there is no justification for the classification of these symptom groups as distinct entities. The use of a proper name to describe a symptom group as a disease entity is also not justified.

5. Of the cases presented 1 can properly be classified as more closely fulfilling the criteria of so-called Reiter's disease. The others must certainly be classified under the heading of erythema multiforme exudativum.

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TRAINING OF A DERMATOLOGIST

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WHAT makes a good dermatologist? Is it the man himself; is it his teacher; is it the institution he attends, or is it the course he pursues? What qualifications should he have to begin the study of dermatology and to enter the practice of the specialty? What can be gained from a review of training in the past? What is the best method of providing the knowledge which he should have to be a firstclass practitioner and consultant? Where should he go to get this knowledge?

These are samples of the questions which have been the concern of those who have had to do with the formulation of standards of specialty training in the last fifteen years.

Every one will agree that the training of the dermatologist, like the training of any specialist, should be based on a broad background of general medicine. It is fundamental to the correct management of a specialist's problems that a good general medical education be a requirement for specialization. I realize in mentioning this obvious necessity that certain restrictions in the educational setup of today are imposed by the element of time, but it is still fundamental that somehow or other this broad background be provided—or required, if necessary—in order to furnish the future specialist viewing only his small portion of the human anatomy with the proper balance for interpreting the events in his special sector in proper relation to the general bodily economy. Graduation from a recognized medical school, preferably in the upper half of the class scholastically, and a one year medical or rotating internship in an approved hospital are obviously minimum requirements for specialization.

For the future dermatologic specialist an additional year or two of general medicine, either on a two year medical internship or by a year or two as a resident on a busy teaching service in a large hospital, furnishes a much more satisfactory preparation for the interpretation of the general relation of the skin. One year of work in a basic science (pathology, chemistry or physiology, for example) related to the dermatologic field will provide an excellent background for a few persons.

Read at the Centennial Celebration of the New York Academy of Medicine before the Section of Dermatology and Syphilology on April 1, 1947.

Certainly, in a few instances, by several years in general practice, in the armed services, Public Health Service or industrial work, for example, such a general background may be provided, but too often habits of study, concentration and investigation, among others, are lost and are difficult to revive or acquire at the later age and after this interim.

THE PAST

Before discussing the training of today and tomorrow let us look back for a moment and take a brief view of dermatologic training in the past. Interest in the skin and its diseases was the earliest requirement for specializing, and ability in the acquirement of experience in the management of cutaneous disease was the earliest mark of a specialist. Of the twenty-nine charter members of the American Dermatological Association, organized in 1876, about two thirds apparently learned their dermatology at home by experience in practice. Only eight members (Bulkley, Duhring, Fox, Heitzman, Jeffries, Keyes, White and Wigglesworth) after graduation from medical school received training abroad in Austria, England, France and Germany before practicing the specialty here. In the next forty years nearly all the men who attained eminence in dermatology went abroad for from six months to three years for study in the specialty. Even with the establishment of dermatologic clinics in this country education abroad was the preferred method of acquiring a knowledge of cutaneous disease. Gradually the dermatologists who had received their training abroad began to take younger men into their offices as assistants and the dermatologic clinics became large enough to furnish satisfactory clinical material. The training was largely on an assistantship basis.

The first residency training in dermatology was established at the New York Skin and Cancer Hospital in 1886. Among the early residents were Fred Wise, Martin Engman Sr. and William Mook. These men were called "house physicians," and the term was for one year. The term "resident" was first used in 1929. A residency was established at the Barnard Free Skin and Cancer Hospital in St. Louis in 1905. The formal training of graduate students in dermatology began at the College of Physicians and Surgeons in 1915. It was on a half time basis. In 1916 such training was started at the University of Pennsylvania in the Graduate School. In 1926, when Dr. George MacKee and his staff joined the New York Post-Graduate Medical School and Hospital, post-graduate training in dermatology was started on a part time basis. In two years it was placed on a full time basis. In 1933 the New York Post-Graduate Medical School and Hospital affiliated with Columbia University and the Skin and Cancer Hospital. The name of the last-mentioned institution had been changed to the

Stuyvesant Square Hospital and became the dermatologic department of the New York Post-Graduate Medical School. Graduate training in dermatology continued on a full time basis.

At the time the American Board of Dermatology and Syphilology was established, in 1932, after much discussion and after consultation with the three already established boards, it was decided that applicants for certification should be required to have at least five years of practice in the specialty, including two full years of special training devoted exclusively to dermatology and syphilology. Furthermore, the candidate was to spend one of these two years in a well recognized clinic or as an assistant in the private practice of a well known dermatologist. For an older group, ten or more years of practice were required, including a satisfactory period of training.

In the first survey of facilities for graduate training in dermatology in this country, in 1935, it was found that there were seventeen institutions which offered three years of training, three which offered two years of training and one which offered one year of training. One other institution offered one year of training in syphilis alone. Among ten of the three year institutions there were offered fourteen residencies, and among five opportunities for thirty-two graduate students. The other three year institutions offered graduates opportunities for training under the title of fellows. There were eighteen opportunities for fellows. Thus there existed 64 openings for dermatologic training which had the approval of the Board.

Beginning in 1940, two years of full time planned training were required by the Board, with adequate instruction in histopathology, mycology, physics of physical therapy and allergy as related to the skin.

In 1944 the three year period of training was established as a requirement. This step had been recommended by the Advisory Board for Medical Specialties some years before with the idea of equalizing, as far as possible, the requirements of the various specialties. Candidates in the armed services were permitted to take the examination at the end of three years' training at this time. In the following year all candidates were given the same privilege. As a part of this three year requirement is the requirement of instruction in the basic sciences as related to dermatology. These are the requirements of today.

THE PRESENT

At the present time there have developed various ways in which a physician may become adequately prepared for specializing in dermatology.

Residencies of three years' duration have been established in large hospitals in connection with beds for the care of patients with cutaneous diseases, sometimes with a separate ward for such patients but often

with the patients scattered about in various wards. A hospital desiring to establish a new residency in dermatology and syphilology is investigated by the Council on Medical Education and Hospitals of the American Medical Association and the Board to determine whether or not adequate training can be provided. The residents live in the hospital, receive a small stipend from hospital funds and have a graded responsibility under the supervision of the dermatologic staff for the care of persons with dermatologic diseases, outpatient and ward, and for consultations on other services in the hospital. Physicians serving in institutions approved for a one or two year residency must arrange for further training in another qualified institution.

Fellows in dermatology in some institutions have almost the same duties and privileges as residents but under a different name. In general, they do not live in the institution, although they may, and they may or may not supervise the actual care of patients. Their stipend is usually higher and often from funds provided for the purpose and not taken from the general funds of the institutions. In the institutions with only one, two or three residents or fellows the teaching, of necessity, is largely on an individual and personal basis.

Graduate students register for a particular course of eight to twelve months' duration given by a medical school, paying a predetermined fee for such a course. They usually have no responsibilities as far as bed patients are concerned, though they may observe and follow their progress. In the institutions with a group of students more teaching is carried on by didactic lectures, classroom exercises and demonstration clinics and there is less intimate contact with patients.

Under the preceptorship system a student may, after the preliminary basic year, serve for one or two years half time as assistant in the office of a qualified dermatologist. At the present time he is required to serve half time in an institution with adequate training facilities. The compensation is arranged between the student and the preceptor. The preceptor must supervise the student's work in the office. It is expected that this student will have had his basic work and the preliminary first year before going to work with a preceptor. This arrangement is comparable to the assistantship of earlier years and requires a close personal relation between instructor and student.

A few persons may receive credit for six to twelve months' work in a special field related to dermatology (pathology, physiology, allergy or psychiatry, for example). This method is of much value in that it can bring to dermatology contributions of interest and importance from the special field.

Then there are the few students who may pursue a miscellaneous course in two or three different places, for example, a one year graduate course followed by a one year residency and perhaps a third year

under a preceptor or in the laboratory. Some duplication of instruction must occur under such conditions, and certain discrepancies will appear. In this type of training much will depend on the student's ability to assimilate the knowledge he has obtained at the various places and to make up any discrepancies in his preparation.

In the Syllabus of Graduate Training[1] issued by the Board are outlined the qualifications by which an institution may be judged concerning its acceptability as a place which provides adequate training. These qualifications were outlined early in the development of the Board and have served a useful purpose in the judging of an institution. Of these items perhaps the most important have been (1) the amount and type of clinical material, observed in both inpatients and outpatients, (2) the ability and size of the teaching staff, (3) the adequate supervision of students, (4) the teaching program and a university affiliation, and (5) the adequate instruction in the basic sciences related to the specialty. Of almost equal importance are (1) the laboratory facilities, (2) clinical and laboratory equipment, and (3) the opportunities for investigative work, while (4) the matter of accessibility to an adequate library and (5) the scientific meetings available are also important.

A recent survey of the institutions providing dermatologic training indicates a notable increase in the opportunities for education in the specialty. The facilities which have been developed for dermatologic training at present, as approved by the Board, are as follows:

Institutions—Type of Training

28 three year residencies

16 two year residencies

7 one year residencies

2 one year residencies (syphilis only)

7 institutions given temporary approval for a one year residency

26 opportunities for fellows

8 opportunities for graduate students

78 preceptors approved to provide training in the last one or two years of a three year period

14 preceptors approved on a temporary emergency basis.

There are approximately 200 physicians in training to specialize in dermatology and syphilology.

These opportunities existing today represent a considerable increase in dermatologic training facilities and, I hope, without any loss in efficiency. A similar expansion in training facilities has taken place in other specialties. It is probable that some of the institutions granted temporary approval for the emergency will be unable to continue to

1. A Syllabus of Graduate Training in Dermatology and Syphilology, 1946, p. 5.

provide proper training because of inadequate clinical material or teaching personnel and will have to be given up.

Some of this increase in facilities is justified in view of the greater civilian demand at present and the fact that there will be more opportunities for specialists in the armed services, the Public Health Service and perhaps in industry or the commercial field. The probable increase in group practice in relatively small communities may also be a factor to be considered in the future over-all picture. It would be unwise, in my opinion, to expand our facilities further. In fact, it is my belief that some applicants for specialty training should be discouraged now and that in from three to five years some deliberate restriction in numbers of students in graduate specialty training should be planned in an attempt to turn them back to general medicine.

THE FUTURE

In planning dermatologic training in the future there are certain aspects which deserve careful consideration by leaders in dermatology and by institutions in which dermatologic training of the highest degree is to be accomplished. Those interested in dermatologic teaching must concern themselves with the student and his selection, with the instructor and his ability to inspire and to teach, with the institution itself and its qualifications for adequate graduate training, with the course of training to be pursued and with preceptors, their qualifications and the method of their selection, among other matters. It is possible that consideration should be given to the training of two types of dermatologists—the first group composed of the larger number of dermatologists who will serve the nation as consultants and teachers and a smaller, much smaller, group made up of exceptional physicians who are destined to become the leaders, especially in investigation and teaching. It is worth our while to consider these aspects in some detail.

The Student.—In the final analysis, the student is the crucial item in any training program. He is the future dermatologist. To furnish him with the necessary training for future practice, teaching and investigation, as well as to provide his future clientele with the highest type of specialist, it is advisable that each student be selected with all possible care. We all know that an able, intelligent, industrious student can reach great heights even with a poor teacher and under poor or mediocre conditions if exposed to good clinical, laboratory and library facilities. A mediocre or poor student will usually fall by the wayside under such conditions. A mediocre, plodding student can be stimulated or dragged along perhaps by a brilliant teacher and a well organized course. It is important that the previous record of a student applying for graduate training, i.e., for example, his record in college, in medical school and

as an intern, should be reviewed with great care. The late Louis B. Wilson,[2] after a long experience in the selection of fellows for the Mayo Clinic, stated that "high relative standing in a superior medical school is probably the most significant educational qualification." A low academic record is, then, a satisfactory reason for discouraging specialization. It is true that personality, however it is judged, and the ability of the person to get along with fellow students and with patients must be given due weight. Ability, initiative, diligence, accuracy and other virtues are of course factors to be considered. The point to be emphasized is the basic importance of the careful selection of every single student for graduate specialty training. Additional emphasis on the importance of the selection of students for specialization was stated by Dr. Albert Key[3] in a recent address as president of the American Orthopedic Association. He indicated briefly the ways in which men have achieved success in later life. He emphasized native intelligence and ability and an unusual capacity for work long and hard over a period of years. He indicated that success has often meant much self-directed study and a continuance of study long beyond the so-called period of training. He emphasized the seizing of opportunities as presented, the finding of a favorable environment for work and the association with men of talent and of knowledge of the subject. He admitted that there may have been occasional fortuitous circumstance or an element of luck but expressed the certainty that hard work and the seizing of opportunities are the main factors. Thus the selection of a high-grade student with a favorable personality, plus hard work on his part, is essential in the background of any program to provide better-trained dermatologists for the future.

The Instructor.—The teaching personnel deserves greater consideration in the future. Adequate time for instruction and supervision of clinical and laboratory work is essential, but it is true that a busy practice often curtails the allotted teaching and hospital time. Most of the teachers in dermatology in the medical schools have demonstrated their dermatologic ability. However, not so much attention has been paid to their ability to teach, to impart knowledge logically and with interest to the student. They have had little instruction in actual teaching. It is true they have had before them in medical school and college many examples of bad to excellent teaching, but little is said about actual methods. Some years ago, in preparing for some statewide lectures on syphilis to general practitioners, a small group was privileged to be coached by an instructor on the staff of a university depart-

2. Wilson, L. B.: Diplomate **14**:75 (Feb.) 1942.

3. Key, J. A.: J. Bone & Joint Surg. **29**:1 (Jan.) 1947.

ment of education. While the repetition of salient features, the careful analysis of the data to be presented and the logical presentation of material stand out as three of the main suggestions, there were numerous details which were emphasized which would be of value to the young instructor, whether dealing with graduate or undergraduate students.

The investigator by nature or because of interest in his work may not be a teacher, but the student should be exposed to the stimulation of his work and his presence even if the interpretation of his work has to be conveyed by the man who is a better teacher. Among the students of today careful observation should be continued by the chief and his corps of instructors to pick out the few who may become the good teachers of the future, and every encouragement should be given to these few to persevere and to progress.

On the practical side it is necessary that provision be made for more adequate compensation for the dermatologist who can inspire students, who likes to teach, who is able to teach and who can analyze and prepare material in a logical, forceful and interesting manner for the students. There are very few full time teachers and investigators in dermatology, and funds to support the development of more full time men would contribute much to the efficiency of supervision of training and should also provide added inspiration and stimulation to the students.

The Institution.—Of prime importance is a separate department under a competent chief. This chief should be a leader in dermatology and an investigator in his own right, with demonstrated ability as an organizer. He will undoubtedly be a certified specialist of the American Board of Dermatology and Syphilology and have a professorial appointment in the affiliated university. It is obvious that under such a chief there should be a competent staff, able, efficient, interested in teaching and sufficient in number for adequate supervision of residents or students. A majority of the staff members should be certified by the Board.

Among other qualifications of an institution qualified for training is the matter of adequate clinical facilities. The estimation of the adequacy of clinical facilities for training purposes is not a simple matter. The difference between 1,000 new patients a year and 800 new patients a year is not the answer. After all, is the total number of new patients the best index of satisfactory clinical facilities? The total number of patients per year is another item to consider. Of considerable importance are the matters of the care with which the patients are studied, the number of instructors and the time provided for teaching, the number of students to be taught under a particular program, the number of beds available for patients to be admitted and observed during the progress of their dermatoses and the extent and carefulness of labora-

tory work, among others. Also to be considered is the number of students being trained. Certainly the observation of 1,000 new patients a year, i.e., 3 to 4 new patients daily, if adequately supervised and with adequate facilities for study, should provide an adequate clinical background for the physician who is to be a consulting specialist. He will have seen in his three years many variations of the common dermatoses and had the opportunity of observing numerous of the rarer conditions.

The need of adequate laboratory facilities and adequate diagnostic and therapeutic equipment for modern dermatologic work is evident. It is, of course, preferable to have such facilities in the department and under the direction of the head of the department, but in some large institutions these facilities are often centralized and funds may be lacking to establish separate facilities in the various departments. However, the chief of the department may be able to develop some way in which such facilities may be utilized by the dermatologic department. The adequate provision of investigative facilities, both clinical and laboratory, is also a necessity in these days. Departmental library facilities are seldom sufficient, but most large hospitals have good libraries and in numerous cities a good medical library is maintained.

A university affiliation is a requisite, since it implies a teaching institution and affiliation with the various basic subjects.

In the matter of bed patients it is important to have adequate provisions for them on a separate ward for dermatologic patients in order that they may have proper nursing care. Patients scattered about on various wards will never have the skilled attention so vital to good progress. The grouping of such persons under a competent head nurse and a dermatologic resident will contribute greatly to their comfort and to their progress, as well as facilitate investigation and instruction.

The Teaching Program.—It is difficult to be dogmatic about a standard program of instruction in dermatology in graduate institutions. Some of the difficulties about a standard teaching program can be better appreciated if the differences in institutions are considered. There are institutions with only one or two residents and with only 900 new patients a year, or with only 9,000 total visits annually to the clinic. Then in a class by itself there is the New York University Post-Graduate Medical School with a staff of 120 physicians and 20,000 new cases a year and 115,000 annual visits, with 50 students. Between these two extremes are institutions with various characteristics. There are institutions with a small number of bed patients and large clinics for ambulatory patients. There are others in which the reverse is true. Thus there must be differences in the teaching program. In the smaller institutions with a few students there will be much personal instruction

by the head of the clinic, both clinical and laboratory, and individual patients will be studied carefully and exhaustively. In the larger institutions didactic lectures, classroom exercises, clinic demonstrations and the like are necessary.

The possibilities of wide variations in instruction are shown further by the handling of the "basic sciences" related to the specialty. There has been some confusion over this term and much discussion over its interpretation, the necessity for the basic sciences and the method of including them in the teaching program. In providing such a requirement the Advisory Board for Medical Specialties and the American Board of Dermatology and Syphilology have had in mind the matter of furnishing a more scientific background for the clinical practice of the specialty. It was not intended that only the material taught to the undergraduate medical students be repeated. The data concerning such sciences as physiology, chemistry, bacteriology and/or pathology relating to the skin should be coordinated and amplified in order to create a better understanding of the fundamental processes of the skin and thus a better explanation of the clinical picture. Likewise knowledge of the fundamental facts, laws and theories of serology, immunity and allergy, for example, is necessary for the specialist in dermatology. Various methods are used in presenting these basic subjects. They are presented in some places by lectures by the dermatologic staff; in other institutions these lectures are given by the instructors on the staffs of the particular basic science departments in the medical school. They are also given in conferences in which the instructors and the students both participate to cover the subjects. This basic work is also covered by considering the various subjects in connection with the related clinical phases as patients are presented for discussion. The Board spent considerable time in developing a syllabus outlining the material to be covered in these fundamental subjects without specifying any particular method of instruction. It is apparent that the same result—a trained dermatologist—may be accomplished in various ways. It is not yet possible to determine the best method. In fact, one student may do better by one method and another be best suited to another system. Individual differences in students and differing internal factors in institutions, however, will continue to maintain differences in teaching programs.

It is easy to understand that the presentation of this basic material along with the clinical case, if there is a sufficiently wide variety of cases, has much to commend it in creating a closer relation between the patient and the scientific phases of disease. However, such a method entails much repetition and a large staff in the larger institutions.

There can be no question in the minds of those who have watched the progress of medicine that today the keys which will unlock the mysteries of many diseases, whether dermatologic or not, lie in the realms of the basic sciences. Not only should there be an expansion of the basic science program in the future but there should be a careful analysis of scientific work being conducted on the fringes of the specialty, with a detailed evaluation of related work in other fields and perhaps the adaptation of work on other organs and cells to the field of cutaneous medicine. Whether the adaptation of teaching methods in other fields, the greater use of visual aids so much discussed at present, or other devices can be of aid in instruction in dermatology are also matters for consideration to future instructors.

In outlining the program for specialty training I felt it best to suggest that the basic subjects be presented in the first of the three years. Last year at the Board meeting it interested me to question a group of the candidates about their training. Certain of the candidates preferred to have most of the basic subjects in the second year, stating that a year of clinical work gave them more pegs to hang this material on and a better understanding of their value and relation. On the other hand, about an equal number preferred to have the basic work concentrated in the first year. There is then apparently as much difference in the minds of the students as there is among the institutions themselves in regard to the place of the basic subjects in the training schedule.

Ill effects of industrial processes on the skin and their prevention are assuming greater importance year by year and deserve more consideration in the curriculum of the future. Syphilis, of course, should be given continued adequate attention. While penicillin has altered the distribution of its care the dermatologist should be equipped to treat this disease and to act as consultant on its many bizarre appearances and the complications of its therapy. Instruction in the psychiatric phases of dermatology should be amplified and the aid of psychiatrists sought in the teaching of psychiatric methods of diagnosis and therapy adapted to the management of cutaneous disease. Dermatologic radiotherapy is firmly grounded in the dermatologic teaching program, but the possible adaptation of new discoveries in this field to the skin and its diseases should be carefully planned. In the field of pediatrics, while there has been much cooperation with pediatricians, a great deal more should be done in teaching the management of cutaneous diseases in the younger age group. Likewise, geriatrics should be given more attention. Studies of the aging skin have been made, but greater emphasis

needs to be placed on the relation of the other organs of the body and other diseases to the cutaneous picture as a part of the passage of years. The relation of general medicine to the skin in this age group can well be amplified.

It is to be realized that the teaching program of any type, with the passage of years and with its new discoveries, becomes cluttered up with relative unessentials and that a periodic review of material and methods is an essential to the formulation of a logical and up-to-date teaching program.

The Preceptor.—The preceptor method of training is the oldest method. The neophyte of twenty years ago or more sought his training under an eminent dermatologist as his preceptor. This preceptor was an outstanding clinician, an investigator, a writer, an experienced teacher. The more famous he became, the more students or preceptees he attracted. Now, while the student may seek the man, times have changed and with the increase in dermatologic practice a greater number of dermatologic practitioners have sought more and more for assistants to help with their practices. In order to be sure that the student will obtain good training and to protect the student against exploitation it has seemed advisable to review with care the applications of dermatologists desiring to become preceptors. Much the same data are required in this case as in the case of institutions. It is necessary to be sure that an adequate number of patients be seen, that adequate supervision be maintained and instruction given and that investigation be stimulated, among other requirements. While this investigation of preceptors will not guarantee good training, it should provide opportunities for certain students to acquire much knowledge of dermatology and to see the practical application of diagnostic and therapeutic procedures. Some students will benefit greatly by the close personal contact with a stimulating preceptor. An additional safeguard to the student is the requirement that half the time be spent in a qualified institution.

As time goes on, the ratings of dermatologists examined by the Board after a period of training under a particular preceptor will provide some measure of the ability of that particular preceptor as a teacher and perhaps contribute to the development of additional criteria for the selection of preceptors.

Of special interest to all who are concerned with the future of dermatology is the matter of selecting and training the exceptionally brilliant physician with a demonstrated investigative ability and an accumulated wide knowledge of general medicine. He may be able to acquire in a shorter period of intensive work the knowledge which will take a much longer time for most students. Some means should be

developed for the acceleration of the training of such persons and the enlistment of institutions and the leaders of dermatology in a plan to provide him with every facility for the acquisition of a most complete and detailed scientific training. These men will be few, but for the future progress of medicine it is to be hoped they can be selected early and aided on their way. The financial and administrative aspects of such a program, because of its individual nature, will be difficult to arrange, but some thought should be given to this problem.

There is considerable comment among physicians in general about the regimentation because of specialty board policies. The establishment of standards of any kind implies a certain amount of regimentation, but there is a definite need for a standard of knowledge to be tested by examination, whereas regulations governing the method of acquiring such knowledge may be termed somewhat arbitrary. In the future it seems to me that more leeway should be provided concerning the methods by which education is attained, with perhaps a compensatory tightening of the standards of certification, perhaps as exemplified by a more searching and perhaps longer examination period. This matter of regimentation has been emphasized for some time by the ophthalmologic board and more recently by Dr. Albert Key of the American Orthopedic Association.

The larger question of the place of the specialty program in American medicine needs consideration. Has this program influenced medical practice unfavorably? If so, how can this influence be altered without sacrificing the benefits derived from the emphasis placed on standards for specialization? Such questions deserve a careful study in the early future.

In conclusion it can be said that the best program for training a dermatologist has not been discovered. The investigation is a continuing one, and the answer is being supplied by the work being done this year, next year and in the years to come. It is evident that adequate training can be obtained by various methods, both in small and in large institutions. The excellence of the end result will depend on the student, the instructors and the institutions and their organization and facilities.

Students should be carefully selected and be provided with three years of well supervised training.

Instructors should be selected for teaching ability and be provided with adequate material and time for teaching.

Institutions to furnish adequate training should have a separate department headed by a competent chief, with adequate clinical and laboratory and investigative facilities.

The teaching program, which will vary to some extent with the institution, must continue clinical training, emphasize the basic sciences related to the specialty, explore further the fringes of the specialty and adapt to its own use pertinent matter in adjacent fields.

The preceptorship system should be developed with great care in the selection of individual preceptors.

Carefully selected students, stimulated by experienced leaders, with hard work under supervision and the proper use of clinical and laboratory materials will provide the community with competent consultants, teachers and investigators.

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HORMONES AND ACNE

A Clinical Evaluation of Hormonal Therapy in Adolescent Girls with Acne

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THE USE of hormones in the treatment of acne is not new. Lawrence and Werthessen [1] in 1942 proposed the thesis that acne is caused by a disturbance of the normal balance between androgens and estrogens. According to their theory, when the unbalance becomes such that there is a preponderance of the androgens, the acnegenic action of the androgens which Hamilton [2] demonstrated is exerted. Urbach [3] in 1939 claimed that the aggravation of acne during the premenstrual phase was due to the presence of an endogenous allergen in the blood of such patients. Apparently Zondek and Bromberg [4] had similar views because they were able to demonstrate by hormone injection a dermal sensitivity not only in asthma, migraine and pruritus vulvae but also in acne vulgaris. On the other hand, MacKenna [5] expressed the belief that Barber and Bishop [6] showed conclusively "that in the causation of acne vulgaris, the secretion and the use of androgens is of paramount importance and that the malady may be cured by the administration of estrogens." Goeckerman [7] reported favorable results following the use of estradiol and diethylstilbestrol in the female and negative results following administration of testosterone to the male.

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Read at the Sixty-Ninth Annual Meeting of the American Dermatological Association, Inc., at Hot Springs, Virginia, May 26, 1949.

1. Lawrence, C. H., and Werthessen, N. T.: Treatment of Acne with Orally Administered Estrogens, J. Clin. Endocrinol. **2**:636, 1942.

2. Hamilton, J. B.: Acne, J. Clin. Endocrinol. **1**:570, 1941.

3. Urbach, E., and Gottleib, P. M.: Allergy, New York, Grune & Stratton, Inc., 1943.

4. Zondek, B., and Bromberg, Y. M.: Endocrine Allergy: Allergic Sensitivity to Endogenous Hormones, J. Allergy **16**:1, 1945.

5. MacKenna, R. M. B.: Dermatology—The International Outlook, J. A. M. A. **135**:1128 (Dec. 27) 1947.

6. Barber and Bishop, cited by MacKenna.[5]

7. Goeckerman, W. A.: Hormonal Therapy of Acne Vulgaris in the Female, Arch. Dermat. & Syph. **61**:237 (Feb.) 1950.

RESULTS OF PREVIOUS WORKERS

Lawrence and Werthessen [1] reported the assays of androgens and estrogens in 33 female patients with acne. The results of the assays indicated significant androgen preponderance as compared to normal standards. No assay of urine from males was reported, for the authors were unable to obtain dependable estrone equivalent values from patients. In a group of 14 female patients, there was none whose menstrual history was normal. Seven complained of severe dysmenorrhea, 8 of hypomenorrhea and 2 of menorrhagia. In 13 there were definite exacerbations of the acne at the time of menstruation, followed by variable improvement, never amounting to complete disappearance, during the intermenstrual interval. The patients were treated either with diethylstilbestrol or with ethinyl estradiol by mouth. Twenty received diethylstilbestrol and 5, ethinyl estradiol. Among the symptoms during the periods of treatment were digestive disturbances, gynecomastia and pigmentation of the nipple.

Fifteen of their 25 patients, or 60 per cent of the series, became entirely free from acne after periods of treatment varying from two to six months. All showed improvement.

Lawrence and Werthessen commented on the high incidence of abnormal menstruation in their series of cases which could not be explained on the theory of chance and which furnished a basis for the belief that acne is associated with an unbalance of hormones.

They emphasized the fact that during catamenia the estrogens are low, while the androgens do not fluctuate significantly. There is therefore a relative estrogen deficiency at the time of exacerbation of the acne at menstruation, and the eruption improves or even disappears in the mild cases as the estrogens increase to their midcycle peak.

These authors stated that if this theory is true, it should be possible to cause the disappearance of acne in a person by producing, by means of therapy, a constant increase in the estrogens in the body of sufficient magnitude to restore the normal dynamic estrogenic-androgen balance. Of importance is their statement that "the close association of acne and masculinizing tumors and the high androgen titers, suggests that an excess of 17 ketosteroids is the determining factor in acnegenesis."

According to First,[8] women normally excrete about three fourths as much androgen as men. This is derived from the adrenal cortex. Since biologic assay is difficult, the chemical assay for the 17-ketosteroids is employed instead. The term "17-ketosteroids" refers to those steroids possessing a ketone group on the seventeenth carbon atom. The principal 17-ketosteroids that occur in the normal human

8. First, A.: Functional Menstrual Disorders: Investigation and Endocrine Therapy, in symposium on Recent Advances in Gynecology and Obstetrics, M. Clin. North America **29**:1375 (Nov.) 1945.

urine are androgenic. Therefore they serve in the female as an index of adrenal function. In female hypogonadism, the 17-ketosteroids may be normal in primary ovarian failure but diminished if the condition is due to pituitary deficiency.

Greenblatt [9] stated that "androgens presumably must play some role in the physiologic economy of the female, otherwise how can we account for the appearance of the same two androgens in the urine of normal women as has been identified in the urine of normal males? Likewise, estrogens are found in the urine of males; in fact, paradoxical as it may seem, an excellent source of certain estrogens is the urine of the stallion." It was first reported by Womack and Koch,[10] in 1932, that the urine of normal women yielded quantities of androgenic material which, as measured by the capon test, was of the same order as that yielded by the urine of normal men. It is quite apparent, therefore, that sex-specific hormones are not peculiar to either sex and that they play an important role in the well-being of the normal adult, both male and female.

HORMONE LEVELS IN NORMAL AND IN ACNEIC PERSONS

There is reason to believe that levels of estrogenic substances in blood and urine are frequently low in patients with acne.

Rosenthal and Kurzrok[11] found that in 34 female patients with acne whose age was 11 to 33 years estrogen was not detected in the urine. Wile, Barney and Bradbury [12] extracted estrogenic substances from the urine of 20 normal women between 15 and 21 years of age and of 12 women of a similar age who had acne. They recognized that the extraction of estrogens was not complete at the low acidity used and stated that the values of 7.7 rat units for the normal and 4.1 rat units for the acneic women represented free rather than total estrogenic substance. Deficiencies other than of the estrogens in men and women must be given consideration.

The studies of Gallagher and associates [13] demonstrated pronounced fluctuations in the daily urinary excretion of androgens and estrogens

9. Greenblatt, R. B.: Androgen Therapy in Women, J. Clin. Endocrinol. **2**:665, 1942.

10. Womack, E. B., and Koch, F. C.: The Testicular Hormone Content of Human Urine, Endocrinology **16**:273, 1932.

11. Rosenthal, T., and Kurzrok, R.: Excretion of Estrin in Acne, Roy. Proc. Soc. Exper. Biol. & Med. **30**:1150, 1933.

12. Wile, U. J.; Barney, B. F., and Bradbury, J. T.: Studies of Sex Hormones in Acne: Preliminary Report on Urinary Excretion of Estrogen, Arch. Dermat. & Syph. **39**:195 (Feb.) 1939.

13. Gallagher, T. F., and others: The Daily Urinary Excretion of Estrogenic and Androgenic Substances by Normal Men and Women, J. Clin. Investigation **16**:695, 1937.

in normal men and women. There is, however, no definite evidence of a monthly cycle in the excretion of either androgens or estrogens in normal men, whereas in normal women the excretion of estrogens is characteristically low during the menstrual flow and normally rises to high levels during the intermenstruum. With the laboratory methods used by Gallagher and co-workers, the average daily excretion of androgens was determined to be 63 to 68 units for the men studied and 42 to 56 units for the women, calculated as international androgen units.

CAUSES OF ACNE (HORMONE)

The glands of the skin are influenced by the male hormone. The appearance of androgens at puberty induces the development of acne in the male, and a similar reaction is noted in patients in whom abnormal androgenic stimulation appears, for example, in patients with tumors of the adrenal cortex. Increased secretory activity of the sebaceous glands is also noted in hypogonadal persons treated with androgens.

Hamilton,[14] in discussing the role of hormones in acne, stated that "despite a correlation between acne and androgens there is no proof that all forms of acne are caused by androgenic substances. Other substances may exert a similar effect and factors beside hormonal unbalance are occasionally of major importance. Presumably causative factors of an infectious, congenital, psychic or dietary nature frequently exist." Steroids of the adrenal cortex, androgenic, estrogenic and luteal substances cause a retention of salt and water. This retention may be an important causative factor and of significance in acne seen near the time of menstruation.

McCarthy and Hunter[15] interpreted their measurements of estrogenic and gonadotropic substances as indicative that the functions of the anterior lobe of the pituitary gland or those of the gonads were deficient in many persons with acne. Hooker and Pfeiffer,[16] as a result of their experiments on the effects of estrogens in the rat, concluded that any reported improvement seen in acne following the administration of an estrogen may be due to the inhibitory effect of the estrogen on the sebaceous glands. According to Obermayer[17] a disturbance in the balance of the sex hormones, with subsequent dysfunction of the liver and poor utilization of vitamin A, may perhaps be one of the

14. Hamilton, J. B.: Acne, J. Clin. Endocrinol. **1**:570, 1941.

15. McCarthy, L., and Hunter, O. B.: Failure of Therapy with Glandular Preparations in Acne Vulgaris, Arch. Dermat. & Syph. **35**:211 (Feb.) 1937.

16. Hooker, C. W., and Pfeiffer, C. A.: Effect of Sex Hormones upon the Rat, J. Endocrinol. **32**:69, 1943.

17. Obermayer, M. E., in discussion on Use of Vitamin A in Treatment of Cutaneous Diseases: Relation to Estrogen and the Vitamin B Complex, Arch. Dermat. & Syph. **58**:64 (July) 1948.

causal factors in acne vulgaris. Hamilton [14] expressed the belief that the full cause of acne is not known but stated that "it is definitely established that one important factor is a relative excess of male hormones."

UNTOWARD EFFECTS OF HORMONE THERAPY

Grollman,[18] in discussing hormone therapy, stated that "although exerting no toxic effects when used in reasonable dosages, the steroidal sex hormones (estrogens, progesterone, testosterone) when administered in large doses over prolonged periods may exert toxic effects in addition to such harmful effects as may follow their physiologic actions when used injudiciously. In the case of the gonadotropins one has to consider the possible deleterious effects of injecting foreign protein as well as the effect of overstimulation of the gonads." Excessive doses may induce irregularities of bleeding in mature women. The carcinogenetic potentiality of the estrogenic hormones, including the synthetic estrogens such as diethylstilbestrol, is of considerable theoretic interest, and this fact should be taken into account in therapeutic applications of these substances. However, as Grollman [19] stated, there is no satisfactory evidence that the estrogens as used therapeutically have initiated cancer in the human being.

Kimbrough and Israel [20] mentioned the dangers of hormone therapy and stated that "the impression has been created that estrogen is carcinogenic, particularly in regard to carcinoma of the breast and uterus. This implication arose from the induction of cancer in experimental animals. In such experimentation, either cancer-susceptible strains or huge doses of estrogen were employed. The results of such laboratory investigations are not directly applicable to man. For instance, it is impossible to administer quantities of estrogens in a human being comparable to those given to experimental animals. Moreover, the clinical evidence of the alleged carcinogenic tendencies of estrogen in the human female is purely clinical and therefore, rather indirect." While there is reason to believe that estrogen per se is not carcinogenic, its use in acne in so-called "cancer families" and in women past the fourth decade of life should be greatly curtailed.

First,[8] referring to the use of testosterone, stated that the danger of producing hirsutism should be kept in mind and may probably be avoided by limitation of the dosage to 300 mg. per month and discontinuance of it as soon as acne is present. Greenblatt [9] stated that pharmacologically effective doses of testosterone propionate which are

18. Grollman, A.: Essentials of Endocrinology, ed. 2, Philadelphia, J. B. Lippincott Company, 1947, p. 577.

19. Grollman,[18] p. 570.

20. Kimbrough, R. A., and Israel, S. L.: The Use and Abuse of Estrogen, J. A. M. A. **138**:1217 (Dec. 25) 1948.

far below the virilizing level were employed in several hundred cases by his group, therapeutic effectiveness (not in acne) having been the result in a goodly number of cases. In more than 100 patients pellets were introduced in doses of 25 to 400 mg. and in not a single instance was masculinization induced. Turner,[21] who treated 54 patients with various types of genital anomalies and dysfunctions with the androgenic hormone, stated that "no untoward by-effects were noted in any of the cases treated."

METHODS OF HORMONE ADMINISTRATION

The methods of administering endocrine products depend on the chemical nature of the hormone and its mode of action in the organism. Some of the hormones are protein-like in composition (parathyroid and pituitary hormones) and hence are digested by the gastrointestinal juices. Such hormones as estradiol and testosterone have uncertain action and are less effective when administered orally.

Many of the sterol derivatives which comprise the male and female sex hormones contain an alcoholic group which is capable of combining with fatty acids. These esters are much more effective therapeutically than the free hormone, and a single injection exerts its effects over a longer period. The implantation under the skin of compressed tablets of crystalline hormones has been found to be exceedingly satisfactory in numerous cases. Since many of the hormones are relatively insoluble in the tissue fluids, their introduction in this way gives a slow but constant absorption of the hormone and a more efficient replacement therapy than it is possible to obtain by other methods.

MATERIALS AND METHODS OF PRESENT STUDY

Three hormones were thought worthy of trial: estradiol, progesterone and testosterone. However, owing to the lack of significant results, estradiol was used less frequently. The intradermic method of injection was selected as the first choice. The determining factor was the work of Urbach,[3] who explained the aggravation of acne during the premenstrual phase as due to the presence in the blood of an endogenous allergen. Also influencing the choice was the work of Zondek and Bromberg,[4] who had ideas similar to Urbach [3] when he routinely injected hormones of ovarian origin such as estrone, estradiol, progesterone and pregnanediol and the androgen or adrenocortical series such as testosterone, androsterone and desoxycorticosterone acetate in pure olive oil. Because he was able by the aforementioned methods to demonstrate a dermal sensitivity to hormones in asthma, migraine, pruritus vulvae, angioneurotic edema, premenstrual disorders and acne, it seemed reasonable to conclude that acne could be explained partially as being on an allergic basis; that is, persons subject to acne were allergic to their own hormones.

21. Turner, H. H.: The Clinical Use of Synthetic Male Sex Hormone, J. Endocrinol. **24**:763, 1939.

DESCRIPTION OF HORMONES USED

A variety of sex hormones have been isolated from tissues and tissue fluids or have been prepared synthetically. They may be classified as: (1) androgens, or male hormones; (2) estrogens, or female hormones, and (3) progestational hormone derived from the corpus luteum.

Progesterone is the active principle produced by the corpus luteum and is characterized by white needle-like crystals with a melting point of 120 to 121 C. It is insoluble in water but soluble in fat solvents. When given parenterally, progesterone is the most potent of the progestins. Anhydrohydroxyprogesterone is a synthetic progesterone which is less effective parenterally but is more effective orally or sublingually than progesterone. Progesterone is metabolized primarily by the liver and excreted in the urine as sodium pregnanediol glucuronidate. In human beings, a deficiency can be noted by endometrial biopsy just prior to the next menstrual period revealing a nonsecretory phase. Unfortunately, the analysis of urine has limitations because pregnanediol has no biologic activity, but the pregnanediol level can be determined gravimetrically according to the technic of Venning and Browne.[22]

α-estradiol is one of the ovarian follicular hormones. It is probably the physiologic one, because it is more active than urinary estrogens, estrone or estriol. In crystalline form, it is insoluble in water but soluble in ether, alcohol, acetone and oil. α-estradiol is the most potent parenteral estrogen and esters have been made—i. e., benzoate, and dipropionate—to prolong activity. Ethinyl estradiol is the oral preparation of choice. The liver is again the primary metabolic site, with estrone and estriol the excretion products. α-estradiol has been isolated from urine of pregnant women. Endometrial biopsy showing proliferation in midcycle would indicate a qualitative test for estrogens. Analytic studies of urine would reveal estrogens only when large quantities are present, i. e., during pregnancy. The biopsy assay methods are more sensitive tests.

Testosterone is regarded as the male testicular hormone. In crystalline form it is insoluble in water and soluble in alcohol, acetone, ether and oil. The melting point is 151 to 154 C. Testosterone propionate is the most active androgen parenterally, surpassing free testosterone. Orally and sublingually, methyltestosterone is most active.

The liver is primarily the metabolic organ. It forms 17-ketosteroids which are excreted in the urine. The diagnosis of a deficiency of testosterone is difficult. Testicular biopsy may be helpful, but its limitations are obvious. Bioassay methods are inadequate because the metabolites are greatly reduced in activity.

Although adrenal cortex preparations were not used in these studies, embryologically there appears to be a close relation between the adrenal

22. Venning, E. H., and Browne, J. S. L.: Studies on Corpus Luteum Function, Endocrinology **21**:711, 1937.

cortex and the sex glands. The two arise from adjacent anlages. The hormones of the sex glands and the adrenal cortex are both steroids which are closely related in their chemical structure. Although necessary for normal reproductive activity, the cortex does not normally exert any demonstrable androgenic activity.

For use in these studies, α-estradiol, progesterone and testosterone were dissolved in propylene glycol in the concentration of 20 mg. per cubic centimeter. Local necrosis occurred in some cases when the preparation was administered intradermally, and it became necessary to change to the subcutaneous route. The varying degrees of pain complained of early in the studies immediately following the injection were eliminated by the addition of 1 per cent ethyl aminobenzoate ("benzocaine"). No untoward reactions occured as the result of a weekly dose (4.0 to 6.6 mg.) of the hormone, except that in some instances, as mentioned later, metrorrhagia and delayed menstruation were noted in a small percentage of patients during their course of progesterone.

For the purpose of testing the role of a dietary influence, all patients, unless previously "dieted," were told to avoid milk chocolate, oranges, nuts, grapes and their by-products over a preliminary period varying from two to six weeks, only a placebo lotion being prescribed. To supply their necessary daily calcium intake, 15 Gm. of calcium gluconate were recommended. Patients responding favorably to dietary and local medication were excluded from these series. In a few instances, patients while receiving injections continued to restrict certain foods from their diet. The results obtained, however, were judged to be independent of diet.

A total of 145 women were treated. These were divided into groups of 100, 25 and 20. Because of the fact that the group of 100 has been under observation over a longer period, it is believed that the figures obtained from it give a more accurate index than those from the two other groups.

ANALYSIS OF PATIENTS IN GROUP 1

Progesterone was used in 95 per cent of the patients, testosterone in 44 per cent and estradiol in 7 per cent. Because of the lack of progress from the use of estradiol, a change in treatment was made for 42 per cent of the patients, with a 59 per cent improvement as the result of such a change. The average number of injections was 17, and the dose varied from 4 to 6.6 mg. of the hormone. An interval of seven days between injections was found to be most satisfactory, and fourteen days, as soon as improvement occurred. Lack of improvement after six injections was followed by a change of therapy.

The average age was 23.37 years, and the duration of the disease, 4.62 years. The dermatosis was limited to the face in 61 per cent of the

cases; in the remainder other body parts were involved such as the neck, chest, back and arms. Roentgen therapy had been previously used with varying degrees of success in 66 per cent of the cases. In 84 per cent the persons had received other forms of therapy, including dietary regulations, injections and ultraviolet irradiation.

Twenty-six per cent of these patients had shown a temporary response to previous therapy, 21 per cent a doubtful response and

Results Following 2,164 Injections of Estradiol, Progesterone and Testosterone in Women

	Series 1 (Way)	Series 2 (Way)	Series 3 (Andrews)
Number of patients treated	100	25	20
Average age, years	23.37	22.52	22.8
Approximate duration, years	4.62	5.25	6.8
Areas affected:			
(1) Face alone	61%	96%	65%
(2) Other parts involved	39%	4%	35%
Previous therapy	84%	88%	60%
Roentgen therapy previously	66%	60%	40%
Response to previous therapy	26%	44%	25%
Percentage of cases influenced by diet	45%	40%	45%
Irregular menses prior to therapy	10%	8%	30%
Irregular menses during therapy	18%	20%	10%
Hormones used:			
Progesterone	95%	96%	100%
Testosterone	44%	20%	0
Estradiol	7%	0	0
Change of therapy	42%	16%	0
Change beneficial	59.52%	50%	0
Average number of injections received per patient.	17.55	7.96	10.5
Dose	3-5 Minims	3-5 Minims	5 Minims
Interval between injections, days	7	7-14	7
Acne worse prior to menses	74%	60%	75%
Known recurrences	25%	8%	15%
Hormone imbalance:			
Present	58%	76%	75%
Absent	38%	24%	15%
Questionable	4%	0	10%
Therapeutic results:			
Good	50%	56%	45%
Fair	22%	24%	30%
None	28%	20%	25%

53 per cent no favorable response. As to dietary treatment, 45 per cent were definitely influenced while 40 per cent were doubtfully affected and 15 per cent were unaffected.

The menses were regular and normal in 90 per cent and irregular and abnormal in 10 per cent prior to hormone therapy. While under treatment, 18 per cent had irregular menstruation. In 74 per cent of the cases, the acne lesions were worse prior to menstruation. In 10 per cent there were abnormal laboratory findings.

RESULTS

The results were judged by the number of acne lesions present at the time of the patient's last visit and the recurrences while she was under observation. The response was good in 50 per cent, fair in 22 per cent and unnoticeable in 28 per cent. Recurrences were noted in 25 per cent, and of these 56 per cent again responded to additional therapy. From an etiologic standpoint, acne in 58 per cent of these patients was believed to be largely the result of endocrine unbalance while other causative factors were present in the remaining 42 per cent.

COMMENT

These studies failed to confirm the theory of Zondek and Bromberg,[4] and Urbach [3] for examples, that acne could be explained from the standpoint of allergy. Kimbrough and Israel[20] stated that estrogen and progestin contain no protein, nor do they per se give rise to allergic manifestations even though they are frequently dispensed in vegetable oils which have been known to evoke sensitization.

Hamilton [14] expressed the belief that the seborrheic action of androgens may be due to (1) a direct action on the sebaceous glands or (2) an indirect action by way of alterations in blood flow, tissue hydration or altered fat metabolism. Of interest and value is his opinion that the fact that the male hormone substance may induce acne in susceptible persons is not proof that the sole cause of acne is the action of the male hormone substance.

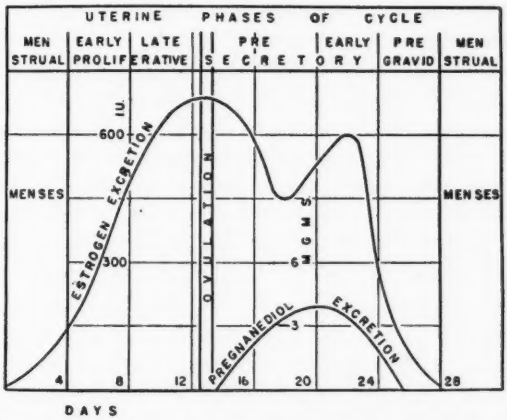
Lawrence and Werthessen [1] commented on the high incidence of abnormal menstruation in their series of cases which could not be explained on the theory of chance and furnished a basis for believing that acne is associated with an unbalance of hormones. The metrorrhagia seen in certain persons while they are receiving progesterone is difficult to understand when one remembers that progesterone is often used because of its depressant effect on uterine motility. Of comparative interest is the fact that large doses of estrogen inhibit established lactation, whereas prolonged treatment with the same hormone induces lactation in the nonlactating breast. Grollman [23] mentioned that small doses of progesterone promptly inhibit menstruation in the monkey and will postpone the menstruation which follows the cessation of estrogen administration. When both estrogen and progesterone are administered at the same time to castrated monkeys, the discontinuance of the progesterone alone is followed by menstrual bleeding. Menstruation accordingly might be looked on as resulting from the retrogression of the corpus luteum with the disappearance of progesterone from the organism.

The results obtained in this series may be explained from several standpoints. In normal women, the excretion of estrogens and preg-

23. Grollman,[18] p. 549.

nanediol is characteristically low prior to and during the menstrual flow and normally rises to high levels during the intermenstruum. Likewise pregnanediol (the excretion product of progesterone) begins to be excreted at the time of ovulation and ceases when the corpus luteum degenerates, which is just prior to the menses. Therefore, both estrogen and progesterone are at low levels when exacerbations in acne usually occur. The improvement in acne occasionally seen during pregnancy may be explained by the fact that the placenta assumes an endocrine function and elaborates estrogenic and progestational hormones as well as its specific hormone, the chorionic gonadotropin.

Assuming that acne does not develop in normal females, one may conclude that those persons benefited by the administration of the female



Curves show the variation in the rate of excretion of estrogen and pregnanediol during the course of the menstrual cycle in women (from Grollman,[18] p. 547).

hormone may have had abnormally low levels whereas those benefited by the male hormone may have had high levels. It seems difficult to believe that androgens in excess are an active factor in the production of acne, and yet our studies in the male and female tend to confirm that impression. Certainly unbalance must exist in many persons with acne. A review of the results causes us to conclude that such an unbalance may be due to a certain hormonal excess in one person and a hormonal deficiency in another. Whether this unbalance is constant is not known although there is reason to believe that an excess may exist at one time and a deficiency at another. In many instances it was possible to control such recurrences by giving small sustaining doses of hormones at intervals varying from two to four weeks and in others at much longer periods.

Stressed is the need for further endocrine studies with special reference to the anterior lobe of the hypophysis because hormones from that lobe govern the cyclic ovarian changes and it is these changes that are responsible for the maturation of the follicle, ovulation, luteinization and maintenance of the corpus luteum.

CONCLUSIONS

These studies emphasized the complexity of acne when viewed purely from an etiologic standpoint. The importance of such contributory factors as diet, especially milk, and the effect of psychogenic disturbances on the endocrine system deserve the greatest consideration. Apparently one's "hormone balance" is more easily upset than is generally believed.

The importance of determining and evaluating the etiologic factors present in each case of acne cannot be overemphasized, and, when possible, therapy should be preceded by a complete physical examination, determination of the basal metabolic rate and studies of the blood.

The statistics obtained in our series clearly demonstrate the value of sex hormones in the treatment of acne vulgaris, and their use seems justifiable when satisfactory results are unobtainable by the commoner methods of therapy. Because of the complexity of endocrine therapy, unless one possesses more than an average knowledge of the subject, collaboration with an internist or endocrinologist is strongly urged.

Ciba Pharmaceutical Products, Inc., supplied the hormone preparations used in these studies.

ABSTRACT OF DISCUSSION

DR. CHARLES C. DENNIE, Kansas City, Mo.: It seems to me that Dr. Way is polishing a facet in a rough diamond. He certainly has approached the problem in a more efficient way than others have hitherto. Dr. Way's paper deals only with acne in the female. Acne in adolescent males compares to that in the female, and if these hormones work in females, why shouldn't they be tried on males?

My associates and I selected only cystic acne in males, those who had had previous treatment with diet, roentgen radiation and penicillin. We followed 12 of these cases through for more than one year. It is my pleasure to report that the use of progesterone in the male produced very beneficial results in the cystic type of acne. These patients were watched carefully, and we particularly noted any change in the character of the sex organs. No deleterious effects whatsoever were noted. The public, having been educated by means of women's magazines and the like, has become alarmed regarding any injection of hormonal substances, fearing a carcinogenic effect. There is no basis for this fear. It is known that in the great majority of acne cases, both in the male and in the female, the acne disappears without treatment after the hormones are balanced. Udo Wile called attention to the deficiency of hormones in both male and female patients with acne.

DR. WILLIAM H. GOECKEKMAN, Los Angeles: I think Dr. Way is to be congratulated on his work in evaluating some of the hormones that he has worked with systematically. There are a number of papers on the biochemistry of acne

with relation to the hormone balance. In a vague way they agree that there is probably some disturbance in these bisexual hormones. I think this question should be before us in an investigative way, particularly from a clinical standpoint. It was for that reason that I presented my paper last year on use of the estrogens in the female. Dr. Way has used α-estradiol, progesterone and testosterone. His results would make me feel only lukewarm. I should approach this subject from a somewhat different manner. I have never used progesterone in acne. However, I have used testosterone in the male about as long as these hormones have been made available to us. If I were asked to state frankly whether or not testosterone had any value in the treatment of acne in the male, I should say it has no value. Quite on the contrary, my results with estrogens in acne in the female have been so surprisingly good that I have to constantly hold down my enthusiasm. I cannot express my enthusiasm sufficiently. Since my results have been so good, it may be of some interest to hear a few of the points I have followed in giving the estrogens. I do not overdose. I am very careful of that. I see to it at all times that the dosage is good and is adequate but that the patient is not made particularly uncomfortable. I usually gave the estrogen in moderate doses but sometimes in large doses, depending on individual response. Routine has no place in this therapy. I put no limitations on local applications or diet except to see that the patient has a fairly sensible diet. So far as carcinogenesis is concerned from this type of therapy, the dose is so small that I think its possibility is negligible. This procedure is not replacement therapy, but it has some effect on the system of which we do not know much. Its action is that of a trigger mechanism. This therapy may eventually prove to be of real value in the treatment of acne. I should like to have this particular work followed through in a determined way. I am sure that hormones will eventually be found to be of a great deal of value in the treatment of acne.

Dr. George C. Andrews, New York: I should like to corroborate the statements that have been made by Dr. Dennie, Dr. Way and Dr. Goeckerman. I feel as Dr. Goeckerman does that the treatment is not a replacement therapy but that small doses of hormones work to adjust something which is out of order or to clear up a maladjustment in some way. When Dr. Way spoke to me about this matter and asked me to try some of these methods at my office, I didn't have much enthusiasm. However, our case records show that some results were startlingly good. I have not used roentgen irradiation in the treatment of acne in well over a year. The results appear to be much better than with roentgen therapy and the old routine therapy. I doubt that I shall ever use roentgen irradiation to treat acne again. I have seen no detrimental effects from estrogenic substances. Small doses over quite a period of time appear to be effective in most cases. Then one can stop treatment and not get any recurrence. This therapy, together with the administration of sulfonamides and antibiotics, is curative in a great majority of cases.

Dr. G. Marshall Crawford, M.D., Brookline, Mass.: During the first half of the menstrual cycle, follicular stimulation occurs and there is a greater amount of estrogen and progesterone produced. The progesterone has a regulating effect on the estrogen. Estrogen is usually converted into estradiol, which is less active but more prolonged in its activity, and into estriol, which is more potent but brief in effect. There is a similarity between the menstrual cycle and the pregnancy cycle. Another factor which may explain a few of the cases in which there was not a good response is the inescapable influence of endometrial necrosis.

DR. CLINTON W. LANE, St. Louis: I was greatly interested in Dr. Way's presentation. I should like to call to your attention a few articles that have been written on this subject, for example one by Weiss and his co-workers. They found that patients with acne had a decreased ratio of estrogen to androgen. In persons with acne it was 2.46 to 6.67 in normal persons. These writers also expressed the belief comedos were due to this decreased ratio. More boys than girls had acne.

There has also been a recent article by Shapiro. He used endocrine creams. A vanishing cream base was employed with sodium estriol sulfate. A decrease of scars and pustules was noted. Acne appeared softer and paler in a period of three to six weeks. Shapiro stated his results were most satisfactory. We might well keep this report in mind although the results are too few for comparison at present. It seems to me the only question that occurs in discussing this article is that just before menstruation, when acne is at its height and estrogen at its lowest ebb, would it not be more logical to employ estrogen than progesterone?

DR. C. J. LUNSFORD, Oakland, Calif.: I have a short statistical report on the local use of an estrogenic hormone in cases of acne in young freshmen women entering the University of California. The cases were not selected. The patients were taken as they came into the clinic, and the condition varied from mild to severe. None of the patients had been previously treated. A menstrual history of each was taken and was not unusual. A general physical examination had been given on their admission to the university. Vaginal smears were not done, but the weight, height and span of each student was noted.

Of the estrogenic hormone cream used, each gram contained 1.25 mg. of the hormone in a vanishing cream base. On investigation this was seen to be about enough to cover the face. The girls were instructed to rub the cream into the skin twice a day after the vigorous use of soap or acidolate® and water. No other treatment was permitted.

Of a total of 45 patients with acne placed on treatment with the cream containing the hormone, 24 cooperated. Then other unselected patients were given the base without the hormone as a hidden control. Five cooperated. All patients, including the controls, were treated from six weeks to four months. Three of the 24 persons who had used the cream containing the hormone claimed some improvement. One of the 5 control patients was enthusiastic about the treatment. Any slight improvement which we were able to detect in any case might easily have been accounted for by the vigorous use of soap and water. In all other cases treatment failed completely.

There were no reactions reported such as swollen breasts or menstrual disturbances.

DR. STUART C. WAY, San Francisco: Although my experience with hormone creams has been somewhat limited, those tried were of doubtful value. In reply to Dr. Goeckerman's inquiry, the results obtained in our series of cases were surprisingly good when one considers that in 84 per cent of the cases previous treatment had failed. As to the percentage helped by each hormone—estradiol, progesterone and testosterone—any necessary figures not found in the accompanying table are available for those interested.

Concerning the merits of chorionic gonadotropin (antuitrin®) in acne vulgaris: although an occasional patient seemed to have been helped by its use, its actual therapeutic value in unselected cases appears problematic.

As to Dr. Lane's suggestion that estrogens instead of progesterone be used prior to the menstrual cycle, they have been tried and found less effective.

RELATIONSHIPS OF SUNLIGHT, COMPLEXION AND HEREDITY TO SKIN CARCINOGENESIS

A. FLETCHER HALL, M.D.
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UNNA ([1894] cited by Blum [1]) is generally credited with being the first to point out that prolonged exposure to sunlight might give rise to malignant tumors of the skin. Hyde (1906),[2] writing "On the Influence of Light in the Production of Cancer of the Skin," brought up the question of "whether actinic rays of light unfavorably influence not all but certain sensitive skin at certain ages of the body, in the direction of the epitheliomatous metamorphosis." He pretty well eliminated heat, wind and frostbite, for example, as causes of skin cancer, by statistics on the prevalence of cancer of the skin in various occupations and in various geographic locations, and concluded: "It would seem that exposure to light and to light exclusively, is the special stimulant provoking a certain proportion of skins to the metamorphosis that means carcinoma." He recognized the role of pigmentation, "especially hyperpigmentation," in the protection of skin from actinic rays, and thus accounted for the relative immunity from cancer of the skin of the Asiatic and African, but he was apparently unaware of the thickness of the stratum corneum as a factor in the protection of skin from light rays. Dubreuilh (1907) [3] also incriminated "chronic exposure to sunlight" as the commonest cause of skin cancer and pointed out that "blonds whose skin is poor in pigment are more affected than brunettes, especially members of the colored race."

Read at the Sixty-Ninth Annual Meeting of the American Dermatological Association, Inc., at Hot Springs, Va., May 25, 1949.

From the Division of Dermatology and Syphilology, Graduate School of Medicine, University of Southern California, and the Los Angeles County Hospital.

Supported in part by the Cancer Teaching Fund of the University of Southern California Medical School, from the United States Public Health Service, National Cancer Institute.

1. Blum, H. F.: Photodynamic Action and Diseases Caused by Light, American Chemical Society Monograph Series, No. 85, New York, Reinhold Publishing Corporation, 1941, p. 252.

2. Hyde, J. N.: On the Influence of Light in the Production of Cancer of the Skin, Am. J. M. Sc. **131**:1, 1906.

3. Dubreuilh, W.: Epithéliomatose d' origine solaire, Ann. de dermat. et. syph. **8**:387, 1907.

Experimentally, malignant tumors of the skin were first produced by ultraviolet radiations by Findlay (1928),[4] who reported that white mice manifested "papillomas and malignant epitheliomas" after eight months of daily three minute exposures to radiation from a mercury vapor lamp. This work has been repeatedly confirmed, with variations, on mice and rats, using light from a mercury vapor lamp and sunlight, with various lengths and intervals of exposure (Findlay, 1930[5]; Putschar and Holtz, 1930[6]; Herlitz, Jundell and Wahlgren, 1931[7]; Roffo, 1933 (mercury arc)[8] and 1934 (sun)[9]; Beard and associates, 1936,[10] and Rusch and Baumann, 1939[11]). By the use of appropriate filters it has been conclusively shown that the carcinogenic rays are those of wavelengths between 2,537 and 3,200 angstrom units (maximum between 2,600 and 3,000 angstrom units) which lie in the same spectral region as those which produce the erythema of "sunburn" and the antirachitic effects of sunlight.[12]

In a recent exhaustive and critical review of the evidence, Blum[12c] concluded: "We now have a number of lines of evidence, all of which converge to indict sunlight as the major cause of cancer of the skin in man."

In 1942, Kirby-Smith, Blum and Grady[14] pointed out that in the albino mouse (the most commonly used experimental animal in the aforementioned investigative work), a large proportion of the rays

4. Findlay, G. M.: Ultra-Violet Light and Skin Cancer, Lancet **2**:1070, 1928; cited by Blum,[1] p. 253.

5. Findlay, G. M.: Cutaneous Papillomata in Rat Following Exposure to Ultra-Violet Light, Lancet **2**:1229, 1930; cited by Blum,[1] p. 253.

6. Putschar, W., and Holtz, F.: Erzeugung von Hautkrebsen bei Ratten durch langdauernde Ultraviolettbestrahlung, Ztschr. f. Krebsforsch. **33**:219, 1930; cited by Blum,[1] p. 253.

7. Herlitz, C. W.; Jundell, I., and Wahlgren, F.: Durch Ultraviolettbestrahlung erzeugte maligne Neubildungen bei weissen Mäusen, Acta pædiat. **10**:321, 1931; cited by Blum,[1] p. 253.

8. Roffo, A. H.: Cancer y sol, Bol. Inst. de med. exper. para el estud. y trat. del cáncer **10**:417, 1933; cited by Blum,[1] p. 253.

9. Roffo, A. H.: Cancer et soliel, Bull. Assoc. franç. p. l'étude cancer **23**:590, 1934; cited by Blum,[1] p. 253.

10. Beard, H. H.; Boggess, T. S., and von Haam, E.: Experimental Production of Malignant Tumors in Albino Rat by Means of Ultraviolet Rays, Am. J. Cancer **27**:257, 1936; cited by Blum,[1] p. 253.

11. Rusch, H. P., and Baumann, C. A.: Tumor Production in Mice with Ultraviolet Irradiation, Am. J. Cancer **35**:55, 1939; cited by Blum,[1] p. 253.

12. (*a*) Roffo.[9] (*b*) Blum, H. F.: Wavelength Dependence of Tumor Induction by Ultraviolet Light, J. Nat. Cancer Inst. **3**:211, 1942. (*c*) Sunlight as a Causal Factor in Cancer of the Skin of Man, ibid. **9**:247, 1948.

13. Footnote deleted on proof.

14. Kirby-Smith, J. S.; Blum, H. F., and Grady, H. G.: Penetration of Ultraviolet Radiation into Skin as a Factor in Carcinogenesis, J. Nat. Cancer Inst. **2**:403, 1942.

under 3,200 angstrom units penetrate to the dermis whereas a relatively small proportion of these short rays reaches the dermis of the human skin, the larger amount being absorbed in the epidermis; this circumstance would seem to explain the great preponderance of sarcomas over carcinomas experimentally produced by light in the relatively thin-skinned mouse (Grady, Blum and Kirby-Smith [15]), contrasted with the rarity of sarcomas and frequency of carcinomas in the case of human beings, whose epidermis is much thicker than that of the mouse.

The ability of carcinogenic rays to penetrate various thicknesses of human skin has been reported on by Blum,[16] who stated that rays of wavelengths under 3,200 angstrom units are completely absorbed within 0.5 mm. of skin thickness; he stated also that 0.08 mm. of epidermis will transmit 44 per cent of rays of a wavelength of 3,000 angstrom units but less than 5 per cent of those with wavelengths under 2,900 angstrom units (the latter figure representing the lower limit of the sun's spectrum). According to Magnusson (cited by Blum [16]), the thickness of the epidermis of the face varies rather insignificantly (0.032 mm. on the forehead, 0.042 mm. on the upper edge of the ear). According to Maximow and Bloom,[17] however, the epidermis varies between 0.07 mm. and 0.12 mm. for the entire body surface except palms and soles, where it varies from 0.8 to 1.4 mm. Covering the discrepancy between these two sets of values, Cowdry and associates [18] gave 0.045 to 0.08 mm. as the average thickness of the epidermis. Thus, authorities can be cited to account for human epidermal thickness all the way from 0.032 mm. to 0.12 mm.; all these thicknesses are much less than 0.5 mm., which Blum [16] stated will absorb all rays of the sun's spectrum under 3,200 angstrom units. In giving values for epidermal thickness, none of the investigators previously cited stated whether or not thickening due to exposure to the sun entered into any of the measurements; this can be an important consideration, inasmuch as Miescher (cited by Blum [16]) showed that the stratum corneum may thicken as much as fivefold or sixfold in response to exposure to ultraviolet radiation. The question of epidermal thickness is further complicated by its normal variation between the suprapapillary plate and the rete peg. In view of all the aforementioned variables it is difficult to accept the suggestion of Lacassagne (cited by Blum [16]) that basal cell carcinoma

15. Grady, H. G.; Blum, H. F., and Kirby-Smith, J. S.: Pathology of Tumors of the External Ear in Mice, Induced by Ultraviolet Radiation, J. Nat. Cancer Inst. **2**:269, 1941.

16. Blum, H. F.: Sunlight and Cancer of the Skin, J. Nat. Cancer Inst. **1**:397, 1940.

17. Maximow, A. A., and Bloom, W.: A Textbook of Histology, ed. 5, Philadelphia, W. B. Saunders Company, 1948, p. 328.

18. Cowdry, E. V.; Cooper, Z., and Smith, W.: Program of Research on Aging of the Skin, J. Gerontol. **2**:31, 1947.

might occur where the epidermis is thin, allowing the carcinogenic rays to penetrate to the basal layer, while the squamous cell type should occur where the epidermis is so thick that most or all the carcinogenic rays are absorbed within it. The suggestion of Stokes, Beerman, and Ingraham,[19] that "thickness of the epidermis, particularly the corneum, on different parts of the face might be of importance in determining the location in skin cancer," might be compatible with the measurements of epidermal thickness previously cited. In this connection it might be pointed out that the stratum corneum and stratum granulosum do not take part in the response to sunlight which eventuates in erythema but act only as filters; thickening of the filter in response to exposure to sunlight might be sufficient to vary the depth of the site of maximum erythema reaction to the rays and thus determine the site of the inception of the neoplastic process or to protect from neoplasia completely by absorption of a sufficient quantum of the carcinogenic rays. It is conceivable that the amount and specificity of the rays of the various wavelengths absorbed determine the type of carcinoma which results or that the absorption of sufficient amounts of carcinogenic rays by the incompletely differentiated cells of an arrested embryonal "primary epithelial germ" (as postulated by Lever[20]) might give rise to the basal cell type of carcinoma or "adnexal carcinoma."

The role of pigment in the protecting and filtering mechanism is apparently not as great as is generally supposed. While pigment may be the most important factor in the protection of the Negro skin from the carcinogenic rays of the sun, it is not for the white skin. In the Negro skin the pigment formed in the basal layer progresses toward the surface and is found in large amounts diffused throughout the squamous cell layer and stratum corneum, where it is in a perfect position to block the carcinogenic rays before they reach the deeper layers of the epidermis. In the white skin, on the other hand, most of what little pigment is formed in the basal layer "drops off" into the dermis and thus does not become interspersed between the surface and the basal layer, where it might contribute some degree of protection. While it is true that some of the pigment finds its way toward the surface, it is not in sufficient concentration in the white skin to afford much protection, and, according to Blum,[21] the principal protective factor is the thickening of the stratum corneum which follows exposure to sunlight. He cited the fact that the transmission of ultraviolet radiation

19. Stokes, J. H.; Beerman, H., and Ingraham, N. R., Jr.: Photodynamic Effects in Dermatology (pt. 2), Am. J. M. Sc. **204**:601, 1942.

20. Lever, W. F.: Pathogenesis of Benign Tumors of the Cutaneous Appendages and of Basal Cell Epithelioma, Arch. Dermat. & Syph. **57**:709 (April) 1948.

21. Blum, H. F.: Physiological and Pathological Effects of Ultraviolet Radiation, Ann. Rev. Physiol. **5**:1, 1943.

by the epidermis of the albino mouse is greatly reduced by repeated exposure of the animal to this agent, in spite of the fact that albinos acquire no melanin; thickening of the stratum corneum, however, does result from such exposure.

It is of interest in this connection to cite Blum [21] on the subject of the formation of pigment resulting from exposure to sunlight. He stated that there are apparently two more or less independent phases, each with a different action spectrum: (*a*) the formation of new pigment, which has the same action spectrum as the erythema of sunburn and probably is a sequel to that process, and (*b*) the darkening of pigment already present in a "bleached" form, on exposure to rays of wavelengths between 3,000 and 4,200 angstrom units (the action spectrum having a rather flat maximum at about 3,400 angstrom units). The latter process requires much greater amounts of radiation than the former and begins almost immediately after exposure instead of after a latent period of a few days; it also depends on the presence of oxygen, whereas the former does not. Miescher and Minder [22] expressed the belief that this darkening represents the oxidation of melanin which is present in a reduced "leukoform" (the process being comparable to the darkening of dead skin by ultraviolet radiation or by heat). Figge [23] showed that melanin behaves as an oxidation-reduction indicator, the oxidized form being dark and the reduced form bleached. The darkening of previously sunburned areas which results from the administration of sex hormones and other agents may be due in part at least to oxidation of reduced melanin. The greater degree of tan which can be obtained from sunlight compared to light from a mercury vapor lamp is due to the greater intensity of rays with wavelengths longer than 3,200 angstrom units in sunlight. Incidentally, it is these rays with longer wavelengths to which workers in tar and pitch become sensitized by anthracene and acridine, and not the carcinogenic rays; if these workers acquire carcinoma of the skin it is either because of a direct carcinogenic effect of the substances in question, independent of light sensitization, or because of the carcinogenic action of rays shorter than 3,200 angstrom units, independent of the substances with which these persons work (Foerster and Schwartz [24]; see also Blum [25]).

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22. Miescher, G., and Minder, H.: Untersuchungen über die durch langwelliges Ultraviolett hervorgerufene Pigmentdunkelung, Strahlentherapie **66**:6, 1939; cited by Blum.[21]

23. Figge, F. H. J.: Melanin: A Natural Reversible Oxidation-Reduction System and Indicator, Proc. Soc. Exper. Biol. & Med. **41**:127, 1939; cited by Blum.[21]

24. Foerster, H. R., and Schwartz, L.: Industrial Dermatitis and Melanosis Due to Photosensitization, Arch. Dermat. & Syph. **39**:55 (Jan.) 1939.

25. Blum,[1] p. 264.

Thus ultraviolet rays were early identified as important factors in carcinogenesis "in certain skins," and pigment production was credited as the body's chief protective mechanism. Somewhat later, thickening of the corneal layer as a response to light exposure was recognized as the primary protective factor, except in the skin of the Negro and Asiatic races. But aside from the frequent observation that Negroes and orientals rarely acquire skin cancer, and the oft repeated statement that "blonds" are more susceptible than "brunettes," the influence of complexion and hereditary "racial stock" was not stressed until Molesworth's observations on "Rodent Ulcer" in Australia were published in 1927.[26] Extensive quotation from his work should be of interest at this point:

> First noted was the large proportion of red and sandy haired patients. But the color of the hair was subsequently found to be undependable as a criterion. For example, brown hair with blue or gray eyes was found very frequently with a very fair skin. In fact the color blue or blue gray of the eyes was much more often associated with such a skin ["a very fair skin"] than was any particular shade of hair.
>
> Another observation was the disproportionate number of Irish and Scottish patients. This is probably explained by the tendency of Scotch-Irish blood to produce red or sandy hair and of Irish to produce that combination of brown hair, blue or gray eyes, with a very fair clear skin (the "Irish beauty type").
>
> People with brown eyes and olive skin very rarely come into the rodent disease list. I have never seen an Italian with rodent disease, nor could Dr. Fiaschi with his large experience recall such an occurrence in his 50 years in Australia.
>
> No instance of a Chinaman or colored patient suffering from rodent ulcer could be found, although many of such people pursue outdoor occupations, generally as market gardeners.

The observations in Germany reported by Stephen Epstein in 1931[27] more or less parallel those of Molesworth. Analyzing a group of 200 patients with epitheliomas (163 basal cell, 13 squamous cell and 24 unclassified) he found twice as many "blonds" and half as many "brunettes" in the carcinoma group as in his control group (395), pointing out the difficulty in classifying many patients, particularly "dark blonds." But even when hair color was disregarded, eye color alone showed a definite tendency toward a large percentage of blue eyes in the carcinoma group. Specifically, he reported that 74 per cent of his carcinoma group had "light eyes" ("blue of various nuances, gray to greenish"), while 62.5 per cent of his control group had light eyes. It is to be noted that while his controls and patients were predominantly light eyed both groups were presumably of central western European extraction, in contrast to Molesworth's material which showed a large proportion of Scotch-Irish-English.

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26. Molesworth, E. H.: Rodent Ulcer, M. J. Australia **1**:878, 1927.

27. Epstein, S.: The Relationship of Hair Color and Skin Color to Skin Epithelioma. Arch. f. Dermat. u. Syph. **164**:304, 1931.

In an excellent paper presented before this Association in 1944 Elliott and Welton[28] pointed out that "There is a certain type of skin which is more fertile soil for the development of epithelioma; namely, that of the person with blond, sandy or ruddy complexion, which freckles readily but does not tan, usually associated with light hair and eyes." These authors also recognized that "in the white skin the pigment itself provides but little protection" from the carcinogenic rays of sunlight.

THE PRESENT STUDY

The present study is concerned with a group of 100 consecutive cases of histologically proved skin carcinoma of the exposed surfaces. Because in it no attempt was anticipated to adduce further evidence in support of the theory that ultraviolet rays cause cancer of the skin in man and because it was primarily concerned with the question of what type of skin is most susceptible to cancer of actinic origin, all cases of carcinoma of the covered skin surfaces and of multiple superficial epitheliomatosis were omitted. The sources of the material were (*a*) the Skin Clinic of the Los Angeles County General Hospital (71 cases) and (*b*) private practice in the Los Angeles "metropolitan area" (29 cases); the cases were accepted for this study in the order in which biopsy specimens were reported as basal cell (58 cases), squamous cell (34 cases) or basosquamous cell (8 cases) carcinoma. When the total reached 100, the series was closed and the present analysis was carried out, based on observations as to color of the eyes and hair and the like and answers to queries regarding such matters as the parents' nationality, color of eyes and history of carcinoma of the skin.

As a control group for certain phases of the investigation was taken the population of patients at the Skin Clinic of Los Angeles County General Hospital on three consecutive days in March 1949; the total was 149, and the cases for the control group were not selected as to age because of the heavy "weighting" which would result from the group with carcinoma of the skin.

A preliminary report on the first 100 cases follows.

Color of Eyes.—In the skin carcinoma group, hereinafter to be referred to as the "carcinoma group," there were 13 patients with brown eyes (dark brown, 6, and light brown, 7) hereinafter to be referred to as "the brown-eyed group," and 87 patients of eye color other than brown (light blue, 53; dark blue, 13; hazel, 16; gray, 3, and green, 2), hereinafter to be referred to as the "blue-eyed group." In the control group, there were 55 (37 per cent) "blue-eyed" and 94 (63 per cent)

28. Elliott, J. A., and Welton, D. G.: Epithelioma: A Report on 1,742 Treated Cases, Arch. Dermat. & Syph. **53**:307 (April) 1946.

"brown-eyed persons." It will be noted that this series shows a much greater differential (87 per cent blue-eyed persons in the carcinoma group as against 37 per cent blue-eyed persons in the control group) than was quoted from Stephen Epstein's series (74 per cent "light-eyed" patients in his carcinoma group as against 62.5 per cent blue-eyed patients in his control group). In both series, however, the high proportion of blue-eyed patients in the carcinoma group is evident.

Hair Color, Past and Present.—In most cases, the patient's word had to be taken for the color of his hair before it became gray or white. In the brown-eyed group the original hair color was given as black in

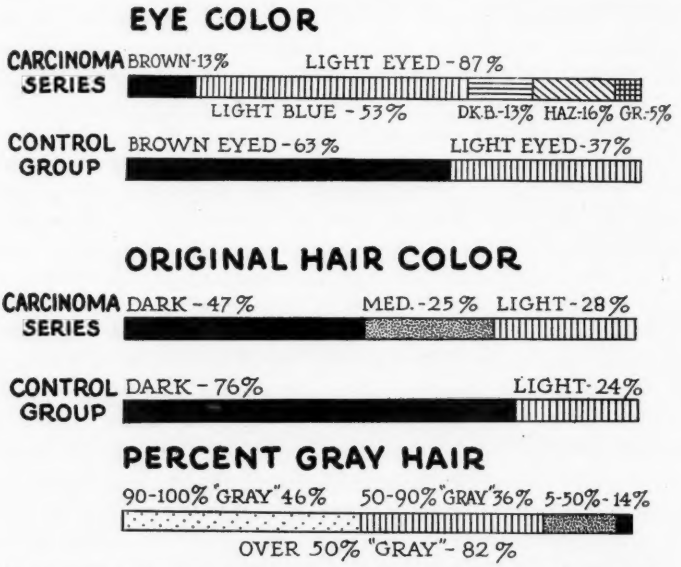

Fig. 1.—Color of eyes and hair for patients with carcinoma and for controls.

6 cases (46 per cent), dark brown in 6 cases (46 per cent) and "dark blond" in 1 case (8 per cent). In this group, at the time of observation, the hair of 4 (31 per cent) was 90 to 100 per cent gray; of 3 (23 per cent), 50 to 90 per cent; of 5 (38.5 per cent), 5 to 50 per cent, and in 1 case the percentage of gray hair was not recorded; the hair of 54 per cent was over 50 per cent gray.

In the blue-eyed group, the original hair color was given as black in 6 cases (7 per cent), dark brown in 29 cases (33 per cent), "dark blond" in 24 cases (27.5 per cent), light blond in 14 cases (16 per cent) and sandy or red in 14 cases (16 per cent). In this group at the time of observation, the hair of 42 (48 per cent) was 90 to 100

per cent gray; of 33 (38 per cent), 50 to 90 per cent gray, of 9 (10 per cent), 5 to 50 per cent gray, and 3 had no gray hair; the hair of 86 per cent was over 50 per cent gray.

As regrouped according to original hair color, in the brown-eyed group 12 had dark hair, 1 had medium dark hair and none had light hair, while in the blue-eyed group 35 had dark hair, 24 had medium hair and 28 had light hair. In the entire carcinoma group, there were 47 dark-haired, 25 medium-haired and 28 light-haired persons (82 per cent of the entire group having hair over 50 per cent gray). In the control group, there were 113 (76 per cent) dark-haired and 36 (24 per cent) light-haired, no "medium-haired" having been designated. The light-haired in both groups (carcinoma and control) approximate each other very closely (28 per cent and 24 per cent respectively) and certainly represent a minority.

Blond is defined in the "New Century Dictionary" as follows: "(a) light colored, as golden or light brown hair; fair haired and fair complexioned, as a person; light in hue, as the complexion." As this definition does not seem to describe the hair color prevailing in this carcinoma group and in view of Molesworth's observations, it seems unjustifiable to continue to propagate the statement that "blonds are especially susceptible to cancer of the skin."

Sex and Exposure to Sunlight.—In the brown-eyed group there were 6 female (46 per cent) and 7 male (54 per cent) patients, while in the blue-eyed group there were 20 female (23 per cent) and 67 male (77 per cent) patients; female patients accounted for 26 per cent of the entire carcinoma group. Nine (70 per cent) of the brown-eyed group and 57 (65.5 per cent) of the blue-eyed group "did outdoor work."

Sex and Type of Carcinoma.—Among the male patients there were 29 (39.2 per cent) squamous cell, 39 (52.7 per cent) basal cell and 6 (8 per cent) basosquamous cell carcinomas. Among the female patients there were 5 (19.2 per cent) squamous cell, 19 (73 per cent) basal cell and 2 (7.7 per cent) basosquamous cell carcinomas.

If cancer of the lower lip (7 cases), which so rarely affects females, is omitted, the figures for male patients become: 22 (32.8 per cent) squamous cell, 39 (58.2 per cent) basal cell and 6 (9 per cent) basosquamous cell carcinomas, the figures for female patients remaining unchanged. Either way, there seems to be a greater tendency to squamous cell carcinomas among males than among females, with a consequent rise in the relative incidence of basal cell lesions among the females.

Ability to Tan.—In the brown-eyed group 7 (54 per cent) stated that they tanned without burning, 5 (38.5 per cent) tanned only after burning and 1 (8 per cent) burned repeatedly without tanning. In

the blue-eyed group, 15 (17 per cent) tanned without burning, 40 (46 per cent) tanned only after burning and 32 (37 per cent) burned repeatedly without tanning. In other words, 46.5 per cent of the brown-eyed group "burned" while 83 per cent of the blue-eyed group "burned."

Ability to Tan and Type of Carcinoma.—Of the basal cell tumors, 20 per cent occurred in persons who tanned without burning, 44 per cent in those who tanned only after burning and 36 per cent in those who burned repeatedly without tanning. These figures so closely parallel those representing the distribution of the entire carcinoma group into the three categories here under consideration (22 per cent, 45 per cent and 33 per cent, respectively) that no significance can be attached

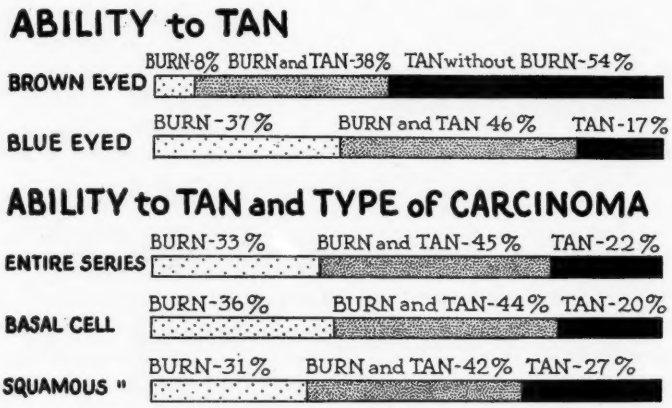

Fig. 2.—Ability to tan and correlation of ability to tan with type of carcinoma for a series of 100 patients.

to them. In a like manner, dividing the squamous cell tumors into the same categories gives figures which again closely parallel those for the entire carcinoma group: 27 per cent occurred in persons who tanned without burning, 42 per cent in those who tanned only after burning and 33 per cent in those who burned repeatedly without tanning. If squamous cell carcinomas of the hand and lower lip are excluded, these values become 21 per cent, 52 per cent and 27 per cent, respectively. In no case does it appear that ability to tan instead of burn repeatedly has any determining influence on what type of carcinoma develops in a given instance. These findings seem to be at variance with the conclusion of Taussig and Williams,[29] if I interpret their

29. Taussig, J., and Williams, G. D.: Skin Color and Skin Cancer, Arch. Path. **30**:721 (Sept.) 1940.

meaning correctly; they stated: "In the cancerous group it was found that some skins redden or redden and darken [in response to the stimulus of sunlight]; others do not. Those who showed this reddening reaction, tend to have the basal celled type of carcinoma, while those who do not so react are more likely to show the squamous celled variety."

Location of Lesion and Type of Carcinoma.—In all, there were 58 (58 per cent) basal cell, 34 (34 per cent) squamous cell and 8 (8 per cent) basosquamous cell carcinomas. In the brown-eyed group there were 10 (77 per cent) basal cell and 3 (23 per cent) squamous cell carcinomas, while in the blue-eyed group there were 48 (55.2 per cent) basal cell, 31 (35.6 per cent) squamous cell and 8 (9.2 per cent) basosquamous cell carcinomas.

In all, there were 14 squamous cell carcinomas of the hands and lower lip (7 of each) and 86 carcinomas of the face, ears and neck, divided as follows: 58 basal cell, 20 squamous cell and 8 basosquamous cell.

Of the lesions affecting the face, ears and neck (i. e., excluding the lesions of the hands and lower lip, which are invariably squamous cell in nature) the brown-eyed group showed 10 (83.3 per cent) basal cell and 2 (16.7 per cent) squamous call; the blue-eyed group showed 48 (64.8 per cent) basal cell, 18 (24.3 per cent) squamous cell and 8 (10.8 per cent) basosquamous cell carcinomas.

Although the brown-eyed group (which "tans" better and therefore averages thicker skin) is too small to be statistically significant, the apparent high incidence of basal cell tumors (83 per cent) compared to that in the blue-eyed group (55.2 per cent) would seem to militate against the suggestion of Lacassagne (cited by Blum [16]) that thicker epidermis (because of a thicker stratum corneum) would be more likely to give rise to squamous cell carcinomas while thinner epidermis would predispose to the basal cell type.

Multiplicity of Carcinomas.—In the brown-eyed group 3 (23 per cent) had one other skin carcinoma present at the time of observation but none gave a history of having had others in the past. In the blue-eyed group 23 (26.4 per cent) had other skin carcinomas present at the time of observation and 20 others (23 per cent) gave a history of (or their records showed) other histologically proved skin carcinomas in the past; 11 of those who had multiple skin carcinomas had had others in the past. Summarizing, 43 (49.4 per cent) of the blue-eyed group (and 46 per cent of the entire series) had or had had other carcinomas of the skin. Of those who had or had had other skin carcinomas, all had at least one blue-eyed parent (so far as could be determined): 24 had 2 blue-eyed parents, 5 had one blue-eyed and one unknown parent and 5 did not know the eye color of either parent; 9 had one blue-eyed and one brown-eyed parent.

The incidence of multiplicity noted here is much higher than that reported by Zola Cooper,[30] who reported only 106 (5.9 per cent) multiple primary carcinomas of the skin among 1,790 cases observed at the Barnard Skin and Cancer Hospital in St. Louis. It is also much higher than the incidence of multiple lesions reported by Phillips[31]: 226 (11.3 per cent) of 2,000 cases of carcinoma of the skin observed in Texas. Elliott and Welton[28] reported 9.6 per cent of their series as having more than one epithelioma when first seen and "in addition 9.7 per cent of all our patients subsequently had one or more additional epitheliomas (not recurrences) and returned to us for treatment." Without allowing for overlapping of these two groups, this would make

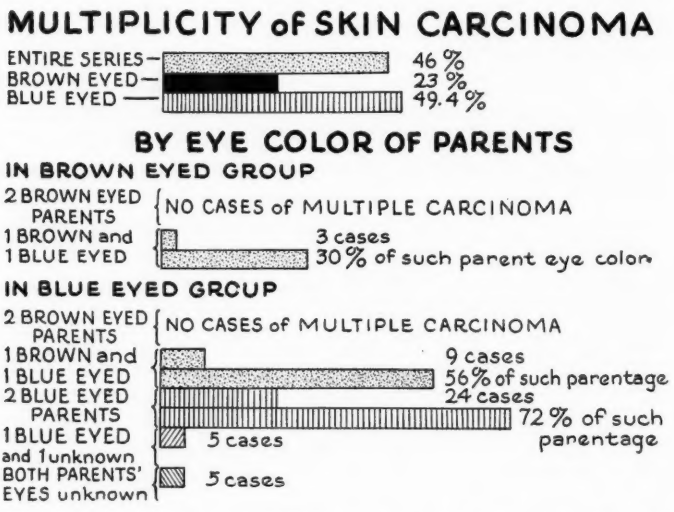
MULTIPLICITY of SKIN CARCINOMA
ENTIRE SERIES— 46 %
BROWN EYED— 23 %
BLUE EYED — 49.4 %
BY EYE COLOR OF PARENTS
IN BROWN EYED GROUP
2 BROWN EYED PARENTS
NO CASES of MULTIPLE CARCINOMA
1 BROWN and 1 BLUE EYED
3 cases
30 % of such parent eye color
IN BLUE EYED GROUP
2 BROWN EYED PARENTS
NO CASES of MULTIPLE CARCINOMA
1 BROWN and 1 BLUE EYED
9 cases
56 % of such parentage
2 BLUE EYED PARENTS
24 cases
72 % of such parentage
1 BLUE EYED and 1 unknown
5 cases
BOTH PARENTS' EYES unknown
5 cases

Fig. 3.—Data concerning multiplicity of skin carcinoma for a series of 100 patients.

an incidence of close to 20 per cent for multiple lesions over a period. These discrepancies may be accounted for by the probability that the Los Angeles area has a higher prevalence rate for skin cancer than the areas in which these other studies were carried out; this may be due to more sunlight with a greater average angle of declination, the proximity to much sand and water and perhaps an older age group (particularly as represented by the clinic group, as is shown later). It would also be explained in part by a greater proportion of blue-eyed people

30. Cooper, Z. K.: A Study of One Hundred and Six Cases of Multiple Primary Skin Cancer, S. Clin. North America **24**:1022, 1944.

31. Phillips, C.: Multiple Skin Carcinoma: A Statistical and Pathologic Study, South. M. J. **35**:583, 1942.

in the group from which the present material was drawn. It must be admitted, of course, that the present series is much smaller than those with which it is being compared and might approximate them more closely if it were continued to a larger total.

Age.—The average age of the clinic group (71 patients) was 72.6 years, while the average age of the patients from private practice (29 patients) was 57.7 years—15 years younger. The average for the entire carcinoma group was 67.6 years.

Eye Color of Parents.—In the brown-eyed group there were only 2 patients (both Mexican) whose parents were both brown eyed; 10 had one brown-eyed parent with the other parent having blue-gray or green eyes; one stated that both parents were gray eyed. Thus it

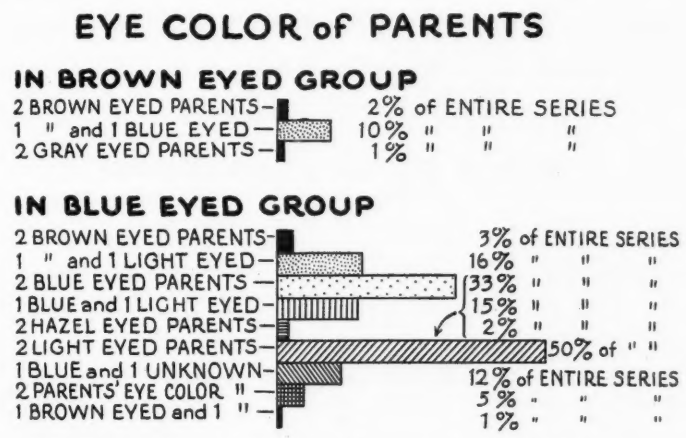
EYE COLOR of PARENTS
IN BROWN EYED GROUP
2 BROWN EYED PARENTS—
1 " and 1 BLUE EYED—
2 GRAY EYED PARENTS—
2% of ENTIRE SERIES
10% " " "
1% " " "
IN BLUE EYED GROUP
2 BROWN EYED PARENTS—
1 " and 1 LIGHT EYED—
2 BLUE EYED PARENTS—
1 BLUE and 1 LIGHT EYED—
2 HAZEL EYED PARENTS—
2 LIGHT EYED PARENTS—
1 BLUE and 1 UNKNOWN—
2 PARENTS' EYE COLOR " —
1 BROWN EYED and 1 " —
3% of ENTIRE SERIES
16% " " "
33% " " "
15% " " "
2% " " "
50% of " "
12% of ENTIRE SERIES
5% " " "
1% " " "

Fig. 4.—Data concerning color of eyes of parents of patients with carcinoma.

appears that only 2 persons in this series of 100 patients with skin carcinoma had no obvious blue-eyed inheritance.

In the blue-eyed group there were 33 whose parents were both blue eyed, and 15 who had one blue-eyed parent and one hazel-eyed, gray-eyed or green-eyed parent; there were 2 who had 2 hazel-eyed parents, while 12 had one blue-eyed parent but did not know the color of the eyes of the other. Thus, at least 50, roughly half of the entire series, had both parents "light-eyed," (of the "blue-eyed group" type). There were 16 who had one "light-eyed" parent and one brown-eyed one. There were 3 in the blue-eyed group both of whose parents were brown eyed, but obviously at least one of each of these pairs of parents carried a blue-eyed inheritance. One patient had one brown-eyed parent but did not know the color of the eyes of the other, while 5 did not know the color of the eyes of either parent.

History of Cancer of the Skin in Parents and Siblings.—In the brown-eyed group there were 2 (15 per cent), 1 of Irish–North European parentage and the other of North European parentage (each having a blue-eyed parent), who gave a family history of skin carcinoma. In the blue-eyed group there were 23 (26.4 per cent) giving such a history; only 2 of these had a brown-eyed parent, the others having both parents with eyes of a light color. In the entire carcinoma group 25 (25 per cent) gave a family history of skin cancer; in Elliott and Welton's series,[28] 29.7 per cent of the 633 patients who were questioned on this point gave such a history.

Nationality of Ancestry.—Each patient was questioned regarding the "extraction" of his parents. In most cases the nationality of two

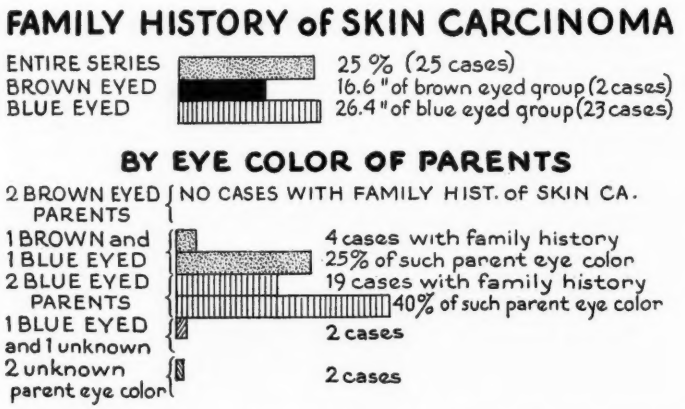
FAMILY HISTORY of SKIN CARCINOMA
ENTIRE SERIES
BROWN EYED
BLUE EYED
25 % (25 cases)
16.6 " of brown eyed group (2 cases)
26.4 " of blue eyed group (23 cases)
BY EYE COLOR OF PARENTS
2 BROWN EYED PARENTS
NO CASES WITH FAMILY HIST. of SKIN CA.
1 BROWN and 1 BLUE EYED
4 cases with family history
25% of such parent eye color
2 BLUE EYED PARENTS
19 cases with family history
40% of such parent eye color
1 BLUE EYED and 1 unknown
2 cases
2 unknown parent eye color
2 cases

Fig. 5.—Family history of skin carcinoma for 100 patients with skin carcinoma.

parents was recorded, but in some instances more than two "extractions" were mentioned (such as "Scotch-Irish-English"), in which all three were included in the listings; this fact accounts for the total of more than 200 for the nationality listings. They were as follows:

Extraction of Parents	Brown-Eyed Group	Blue-Eyed Group	Total
Irish	6	52	58
English	2	41	43
Scotch	1	41	42
North European	8	21	29
Central European	1	13	14
Scandinavian	0	9	9
Mexican	8	0	8
Amerind	0	1	1

It is at once evident that the British Isles account for a two-thirds majority (143 of 214) of the parentage of all the carcinoma group while the so-called Caucasian group accounts for 96 per cent of the extraction listings (205 of 214). These figures take on added significance when it is noted that the control group included only 59 per cent "Caucasians" and 41 per cent Mexican, Negro and Japanese.

In this connection it is of interest to refer to the observations of Schrek,[32] who in an analysis of 20 cases of skin carcinoma in Negroes reported that although carcinoma of the exposed skin is much less frequent in Negroes than in the white race, carcinoma of the covered skin areas has the same incidence in the two races; he also pointed out that in the white race cutaneous cancer is more prevalent in southern than in northern states but that in Negroes the incidence is not affected by geographic factors. These interesting conclusions suggest

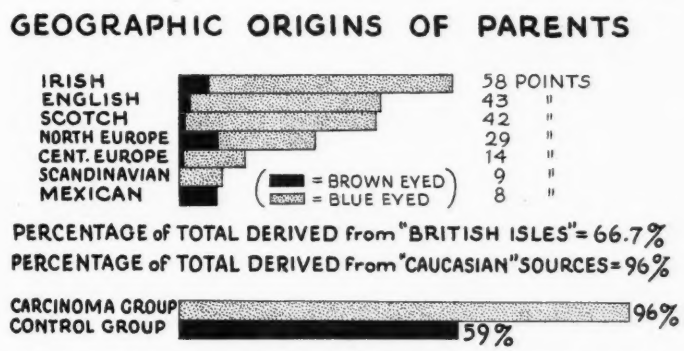

Fig. 6.—Origins of parents of patients with carcinoma and of controls.

that sunlight is not an important (if any) factor in the production of cutaneous carcinoma in the Negro race; the figures reported in the preceding paragraphs might be considered evidence in favor of extending that suggestion to include Mexican, Oriental and perhaps all homozygous dark-eyed persons.

COMMENT ON THE PRESENT SERIES

Color of Eyes.—Although drawn from a population predominantly brown eyed, it was found that 87 per cent of 100 consecutive patients with histologically proved carcinoma of the exposed surfaces of the skin had eyes of light color, other than brown.

Color of Hair.—In the entire group of 100, 47 were originally dark haired, 25 medium haired and 28 light haired, 82 having hair over 50

32. Schrek, R.: Cutaneous Carcinoma: An Analysis of Twenty Cases in Negroes, Cancer Research **4**:119, 1944.

per cent gray at the time of observation. It does not seem appropriate to refer to such a group as predominantly "blond," and it is suggested that this term no longer be used to characterize the type of person whose skin is particularly susceptible to cutaneous malignant growths. A large percentage of "gray hair," however, was noted in the carcinoma series; but in the absence of appropriate control figures involving the same age group, no definite conclusions can be drawn in this regard.

Sex and Exposure to Sunlight.—The brown-eyed group consisted of 46 per cent female and 54 per cent male patients, as against 23 per cent female and 77 per cent male patients in the blue-eyed group. This could be construed as evidence that sunlight may not play as large a part in carcinogenesis in the brown-eyed group as in the blue-eyed group, although about the same percentage of both groups (70 per cent and 65.5 per cent, respectively) stated that they did "outdoor work."

Sex and Type of Carcinoma.—The higher incidence of the squamous cell type of carcinoma among male as compared with female patients (39.2 per cent in comparison with 19.2 per cent) found in this series is comparable to the findings of others, for example, Lunsford and Taussig.[33]

Ability to Tan.—Only 46 per cent of the brown-eyed group ever "burned," while 83 per cent of the blue-eyed group "burned"; only 8 per cent of the brown-eyed group never tanned, while 37 per cent of the blue-eyed persons never tanned. Here again there is an implication that sun may not be as important a carcinogenic factor among brown-eyed people as among blue-eyed ones.

Ability to Tan and Type of Carcinoma.—It does not appear from this series that ability or inability to tan is a determining factor with regard to the histologic type of carcinoma which will develop.

Location of Lesion and Type of Carcinoma.—As is usually found to be the case, all the lesions on the lower lip (7) and dorsa of the hands (7) were of the squamous cell type. There was a higher incidence of basal cell lesions among the brown-eyed (presumably "thicker-skinned") patients than among the blue-eyed ones; this is the reverse of what one would expect according to the conjecture of Lacassagne as mentioned previously.

Multiplicity of Carcinomas.—The incidence of multiple carcinomas was much higher in this series than in previously reported studies, and possible explanations for the discrepancies have been offered. Further attention to this category brings forth some points of interest.

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33. Lunsford, C. J., and Taussig, L.: Superficial Epitheliomata, California & West. Med. **25**:740, 1926.

In the brown-eyed group, 23 per cent had or had had other skin carcinomas, while 49.4 per cent of the blue-eyed group were so affected. All those having multiple lesions, past or present, had at least one blue-eyed parent (so far as could be determined), and in at least half of this group both parents were blue eyed. Furthermore, of the 33 patients in the entire carcinoma group who had two blue-eyed parents, 24 had multiple carcinomas of the skin, past or present. These observations suggest that the inheritance of special susceptibility to cutaneous malignant growths may be in some way related to the inheritance of blue eyes or that the inheritance of protective mechanisms against the carcinogenic rays of the sun may be related to the inheritance of brown eyes; a large proportion of those without brown-eyed inheritance (24 of 33, or 73 per cent) who had skin cancer had multiple skin cancers by the time they came under observation for this study.

Color of Eyes of Parents.—There were only 2 patients in the entire carcinoma group of 100 who had no obvious blue-eyed inheritance; this number represents such a small proportion as to make it commensurate with the incidence of carcinoma of the skin on covered parts of the body and hence not necessarily related to carcinogenic rays of sunlight. On the other hand, at least 50 per cent of the entire series were the offspring of 2 light-eyed parents, while the rest had one light-eyed parent. Here again is the suggestion that eye color has some genetic relation to susceptibility to or protection from "light-caused" skin carcinoma.

History of Skin Cancer in Parents and Siblings.—No patient with two brown-eyed parents gave a family history of carcinoma of the skin, and only 4 with one brown-eyed parent gave such a history, while 21 who gave a family history of carcinoma of the skin had 2 blue-eyed parents. This point adds further weight to the suggestions which were developed in the two preceding paragraphs.

Nationality of Ancestors.—The lineage of two thirds of the carcinoma group was traced to the British Isles: England, Ireland and Scotland, although persons with this lineage do not predominate in the population from which this series of cases was derived. Other sources of predominantly blue-eyed types, such as the Scandinavian countries, Northern Germany and Northern France, are not so well represented in the carcinoma series.

SUMMARY

The observations brought forth in this study suggest that the more brown-eyed inheritance a person possesses, the better protected he is from the carcinogenic rays of the sun. Blue-eyed children of blue-eyed parents, are, in general, the most susceptible as a group, but many

of these are capable of tanning without repeated burning and thus acquire a fair degree of immunity.

Superimposed on the classification of relative susceptibility according to inheritance of eye color is another factor which seems to be racial, although it involves mainly the blue-eyed group: descendants of natives of the British Isles, particularly when blue eyed, often exhibit an almost complete inability to acquire and retain a thick enough stratum corneum to protect them from rays of carcinogenic wavelengths in the amounts encountered in such regions as Texas, Arizona, Southern California and Australia.

It can be conjectured that this very inability to acquire and retain a thickened stratum corneum was of definite survival value in the British Isles before the advent of vitamin D, because it allowed a greater absorption of rays of the wavelengths in question, which are also antirachitic; relatively small amounts of these rays are available in the British Isles, and there is little threat of carcinogenesis. It is to be remembered that other regions as far north of the equator as the British Isles have ice and snow which reflect the rays in question during the winter months, thus supplementing the small amounts of antirachitic rays available, while the year-round verdure of the British Isles absorbs them; thus the Scandinavians and Russians, for example, can afford to tan somewhat and still get enough antirachitic effect in their native habitat. When they migrate south, their ability to tan protects them from the carcinogenic amounts of the wavelengths in question.

CONCLUSIONS

Consideration of the results of the present study, in conjunction with the observations of others cited, leads to several conjectures:

1. There are certain racial stocks and hereditary complexion patterns in which sunlight is not an important, if any, factor in skin carcinogenesis; these include certainly the Negro and Oriental races, probably the Mexican and Mediterranean and possibly all homozygous brown-eyed persons.

2. There are certain racial stocks and hereditary complexion patterns in which sunlight is by far the most important carcinogenic factor, when repeatedly encountered in erythema-producing quantities; these include certainly those of Irish-Scotch-English ancestry, probably the blue-eyed North Europeans, including the Scandinavian, and possibly all homozygous blue-eyed persons.

710 Wilshire Boulevard.

Dr. Harry Leavitt and Dr. Otto Hannebaum collected the data on the clinic cases. Miss Avis Gregersen prepared the pathologic sections, and Dr. L. H. Winer interpreted them.

ABSTRACT OF DISCUSSION

DR. JOSEPH A. ELLIOTT, Charlotte, N. C.: Dr. Hall has made out a good case for the concept of a consistent relation borne by sunlight, complexion and heredity to skin carcinogenesis. I am sure we all heartily agree with his summing-up that for certain racial stocks and for persons of certain hereditary complexions, sunlight has no great part in the production of cancer of the skin and, conversely, that in the case of certain other racial stocks and persons of certain other hereditary complexions, sunlight has most to do with the causation of skin cancer. It would seem, indeed, that the disclosures of Dr. Hall's painstaking, well controlled investigation would justify him in applying to his statements a good deal stronger term than "conjectures."

Rather than go over and reemphasize details of Dr. Hall's excellent piece of work, it occurs to me to say something on a matter which appears to be related, a further study of which may enlarge our understanding of the relation between exposure to the sun's rays and the occurrence of cancer in the skin.

Some weeks ago, I chanced to hear over the radio a fragment of a program which dealt with photosensitization produced in cattle, sheep and horses that had eaten Klamath weed. It was stated that Hypericum perforatum, St. Johnswort, or Klamath weed, as it is called on the Pacific coast, has become a serious economic problem to the cattle and sheep raisers in the California area. The problem has become sufficiently grave to warrant the United States Government's attempting to eradicate the weed. By importing a certain type of beetle which feeds on this weed, the Department of Agriculture is trying with some success to solve the problem. Having a special interest in photosensitization I applied to the Department of Agriculture for further information. In response there came to me Bulletin No. 202, September 1930.

In this bulletin there is quotation from an Italian publication of 1787: "Hypericum crispum; a quick poison of white sheep, so that all which graze in the Tarentine fields are black." Also, a Signore Manni is quoted as saying, "The plant injured only white sheep; when eating in the morning, they get their chins and lips wet with frost, rub the chins and lips on various parts of the body and in a few days the wool falls off, the face swells, and there is an irritation over the whole body surface."

To cite further from Bulletin No. 202: In 1843 Torrey wrote, "This pernicious weed (Hypericum perforatum, St. Johnswort) causes sores on the skin, especially in animals whose noses and feet are white." A number of others noted that only white animals, or those having white spots, were affected. In 1849 Verheyen (Belgium) was the first to connect the effects of these plants with the influence of the sun.

Chestnut (1898) wrote that Hypericum was commonly believed to cause eruptions on the udders of cows and on the feet of white-haired animals. Chestnut cited Brady as saying that in his experience only white areas were affected.

Henry (France, 1910) recorded specifically that white-skinned animals that were protected from the light are not affected by the plant and that the Arabs stain the skins of their animals with solutions of tobacco or henna and thus protect them.

Ray isolated a red fluorescent substance from Hypericum perforatum which acts as a sensitizing agent to light. He was able to produce the disease in animals by feeding them this pigment.

Henry stated that buckwheat will produce similar symptoms in animals under similar conditions. He further stated that buckwheat contains a fluorescent substance which is toxic to animals when they are exposed to the ultraviolet rays of

the sun. He performed a series of experiments to test the possibility of contact poisoning by Hypericum perforatum, the results of which indicated that such poisoning never occurs.

I suggest the likelihood of sensitization of white and partly white animals to the sun's rays by the systemic effect of members of the family Hypericum, buckwheat and other plants and, further, the possibility or even the probability of materially advancing our knowledge of selective susceptibility of light-skinned human beings to cancer of the skin by following this lead.

DR. MARION B. SULZBERGER, New York: I enjoyed this important paper of Dr. Hall's and also Dr. Elliott's fine discussion. It is not astonishing when one hears a contribution from sunny California to learn that light-eyed persons are more susceptible to carcinoma than are dark-eyed ones. As Dr. Hall stated, it has been pointed out previously that the eye color is the most important factor here rather than just the color of the hair or skin. Stephen Epstein, for example, noted exactly the same relation between blue eyes and carcinoma even in the population around Breslau, a region of Germany which certainly cannot be characterized as particularly sunny. We might conclude from these studies that perhaps for persons with certain occupations such as range riders or cowboys, we should choose brown-eyed persons with brown-eyed parents. It has seemed to me that dark-eyed persons may also be less susceptible to solar sensitization and carcinogenesis from substances such as shale, tars, pitch, railroad ties and oils. Perhaps industry should (when feasible) choose brown-eyed persons with two brown-eyed parents for occupations requiring the handling of these substances and other notorious skin carcinogenic agents.

DR. PAUL E. BECHET, Elizabeth, N. J.: Dr. Hall chose a most interesting subject for his initial presentation before our Association. The clinical and experimental evidence that excessive exposure to sunlight is an important factor in the causation of skin cancer has been proved by many observers and is so overwhelming as to force acceptance. I am somewhat surprised that Dr. Hall stated that blonds are not especially susceptible but that blue-eyed and thin-skinned people are, regardless of the color of their hair. This statement is against the opinion of the majority of writers on the subject. McCoy (Solar Keratoses and Cutaneous Cancer, ARCH. DERMAT. & SYPH. **1**:175 [Feb.] 1920) found that in his private practice 62 per cent of the cases of cancer occurred in blonds, 31 per cent in persons with auburn hair, and only 7 per cent in people with dark hair and skins. Molesworth [26] stated that the Scotch-Irish inhabitants in Australia, with their light hair and skin, were particularly susceptible. In the large number of cancers of the skin observed by me from 1909 to 1934 at the New York Skin and Cancer Hospital, epitheliomas were observed far less frequently in brunets than in blonds (Bechet, P. E.: Excessive Solar and Phototherapeutic Irradiation, ARCH. DERMAT. & SYPH. **29**:221 [Feb.] 1934).

Animal experimentation by Putschar and Holtz [6] proved the incidence of cancer of the skin after prolonged ultraviolet irradiation from mercury vapor–quartz lamps; the exposed rats, after the twenty-eighth week, acquired many epitheliomas of the basal and mixed type, some keratoses and cutaneous horns. One of our own, James Nevins Hyde, was the first to call attention to excessive exposure to the sun as an etiologic factor in cutaneous cancer,[2] one year before Dubreuilh's article on the same subject.[3] I think it is the prior changes in the skin (dryness, atrophy, telangiectasia and pigmentation) induced by years of excessive exposure to sunlight which are most responsible in carcinogenesis of the skin. Even solar infra-red rays may also play a part. I recall a clerk at a department store who suffered a contusion on the back of one hand and was forgotten by the nurse at the store for

about an hour while undergoing treatment under an infra-red lamp. As a result her skin, over a year later, showed pronounced atrophy and telangiectasia, indistinguishable from a mild radiodermatitis.

I greatly enjoyed Dr. Hall's paper.

DR. GEORGE C. ANDREWS, New York: I enjoyed Dr. Hall's paper also. It would seem, however, that his statistics are based on rather a small group. The reason I mention this is that most statistics on this same matter are based on small groups. We should really have thousands of cases to form any general conclusion. I want to call your attention to the article by Piers in the *British Journal of Dermatology* (**60**:319 [Oct.] 1948) about skin cancer in Kenya Colony. When we speak of fair-skinned persons, we usually are speaking of blond, blue-eyed people. Of course, when we are born, we all have blue eyes which later change to dark. It is perfectly possible that the brunet skin is a structurally tougher skin phylogenetically than the blond skin. The skin of blond and blue-eyed persons is not structurally as complete or as well developed as is that of brunets. Perhaps we should, in this connection, think of the developmental traits of such skins and also think of age. We should like to know the age of these patients. I personally know of a cancer of the skin in a brunet who is dark eyed and had dark-eyed parents. This work is interesting, and Dr. Hall should be congratulated for pursuing it. I hope he will gather a larger number of statistics and report later.

DR. FRANCIS A. ELLIS, Baltimore: I do not think that Dr. Hall mentioned what percentage of his group had basal cell lesions. Walter F. Lever (Pathogenesis of Benign Tumors of Cutaneous Appendages and of Basal Cell Epithelioma: I. Benign Tumors of the Cutaneous Appendages, ARCH. DERMAT. & SYPH. **57**:679-708 [April] 1948; footnote 20) claimed that basal cell epitheliomas are hamartomas. Do blonds have a higher percentage of these hamartomas than brunets? Why do Negroes have so few basal cell epitheliomas if these lesions are hamartomas?

DR. LOUIS A. BRUNSTING, Rochester, Minn.: It has been shown that carcinoma of the skin is especially likely to develop in blue-eyed persons with a fair complexion; on the basis of clinical impression, I should include red-headed persons in the same category. One or two questions come to mind. Does the mechanism of pigmentation influence the cycle of keratinization? The two are affected by such diverse stimuli as radiant energy externally and arsenic internally. In the consideration of developmental differences of keratinization, does such a condition as ichthyosis influence the tendency toward spontaneous carcinogenesis?

DR. A. FLETCHER HALL, Santa Monica, Calif.: I certainly appreciate the kind discussions. I was much interested in Dr. Elliott's mention of St. Johnswort and its photosensitizing effect on white-haired animals. This was treated in considerable detail by Blum in his monograph "Photodynamic Action and Diseases Caused by Light," [1] which I used extensively for my groundwork in this study. As regards Dr. Sulzberger's remarks that perhaps we should choose brown-eyed people to work with pitch and shale oil, for example, my paper as written for publication quotes Foerster and Schwartz to the effect that an entirely different wavelength band is involved in the sensitization of the skin to the sun by the substances that are involved in the pitch and shale oil. It is their conclusion that these substances sensitize to a different spectral band than the carcinogenic band and therefore produce carcinogenic effects chemically rather than through sensitization to the sun.

In regard to Dr. Bechet's remarks, the dictionary definition of blond seems always to mention light hair coloring as well as lightness of complexion. It would appear that individuals with blond skin, regardless of hair color, are more suscep-

tible, but they usually have blue eyes. Women of the Irish beauty type with black hair and blue eyes are extremely susceptible to sunburn and carcinoma of the skin. The article by Schrek [32] dealing with the incidence of carcinoma of the skin among Negroes is of interest in this regard. Schrek pointed out that skin carcinoma of the exposed surfaces tended to be much more frequent in the white race than in the Negro race, while carcinoma of the covered skin surfaces had the same incidence in the white and Negro races. He also pointed out that the incidence of skin carcinoma is much greater in the South than in the North in the white race but that no difference was noted in the geographic incidence among Negroes. We excluded the Bowen old type of carcinoma and multiple superficial epitheliomatosis from our series, as we were concerned only with lesions which could have been caused by sunlight. I am in complete agreement with Dr. Andrews' statement that this is a small series of cases. We had only 13 brown-eyed persons, for example, which is an inadequate number from which to draw any conclusions regarding factors within the brown-eyed group; it can be used only for contrast with the blue-eyed group. I hope to continue this study to include a statistically significant number. The average age of our group was 67.6 years; it is of interest to note, in this regard, that it has shown in experimental animals, at least, that the incidence of actinogenic carcinoma depends not so much on age per series as on the number and duration of and frequency of exposure to the carcinogenic rays. As to the percentage of basal cell lesions, there were 58 per cent basal cell, 34 per cent squamous cell and 8 per cent basosquamous cell carcinomas. Interestingly enough and contrary to what one might expect, the brown-eyed group had a higher percentage of basal cell lesions than did the blue-eyed persons; one might expect brown-eyed persons with thicker skin to be more likely to acquire squamous cell carcinoma. The question of the influence of thickness of skin, brought up by Dr. Jacob, is an extremely difficult one to evaluate because of technical problems; it is the next "nut we hope to crack."

"PROPHETIC" PATCH TEST

Report on Results of Some 14,000 Completed Tests Performed by the Army Industrial Hygiene Laboratory

LIEUTENANT COLONEL B. DIXON HOLLAND *

COLONEL WESLEY C. COX

Commanding Officer, Army Industrial Hygiene Laboratory, Army Chemical Center, Md.

AND

LIEUTENANT COLONEL EDWARD J. DEHNE

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MEDICAL CORPS, UNITED STATES ARMY

THE ARMY Industrial Hygiene Laboratory applied 28,201 test patches to 2,036 volunteer human test subjects during the period March 1948 to April 1949 in the "prophetic" patch testing of various items of military supplies and equipment destined for contact with the skin of personnel of the armed forces. In addition to the standard, cellophane-backed, elastic adhesive patch, known as the Schwartz patch, two other devices, to be described, were tried experimentally for holding the test materials in contact with the skin, in an effort to make the conditions surrounding the testing of an item correspond more closely with conditions surrounding the use of that item. Materials tested included leathers, fabrics and plastics treated with chemicals to render them resistant to mildew, fabrics treated with chemicals to make them resistant to shrinkage, natural and butyl rubbers for gas masks, gauze impregnated with antiseptic solutions and untreated or widely accepted materials to serve as controls.

TECHNIC AND TIMETABLE EMPLOYED

The technic and timetable followed in this testing were essentially those recommended by Schwartz, Tulipan and Peck [1] in describing the prophetic patch test, with substitution of a band and the Army Industrial Hygiene Laboratory (AIHL) patch for the Schwartz patch in certain instances. On the first day a square-inch piece of the test material is applied to the skin and held in place with an adhesive patch or nonadhesive band; on the third day the patch or band is removed and left off and the test site is observed for reaction; on the fourth day the test site is again observed for reaction; on the fifteenth day a similar patch of the same material is again applied to approximately the same area of skin and held in place as before.

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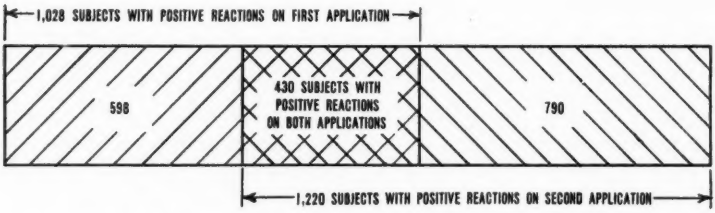
1. Schwartz, L.; Tulipan, L., and Peck, S. M.: Occupational Diseases of the Skin, ed. 2, Philadelphia, Lea & Febiger, 1947.

and on the seventeenth and eighteenth days the same steps are taken as on the third and fourth days respectively. The forty-eight hour readings, i. e., those on the fifth and nineteenth days, were discontinued after the first few months.

The classification of reactions has been made according to the following scale used by Schwartz, Tulipan and Peck [1] : negative (0), no reaction; questionable (?), erythema too faint for one to call the reaction positive; 1 plus (+), clearcut erythema; 2 plus (++), erythema plus edema or papules, and 3 plus (+++), erythema plus edema plus vesiculation.

The purpose of the prophetic patch test has been to predict the proportion and severity of the reactions which the tested materials, such as leathers, plastics or fabrics, would give when put to their normal or intended use, e. g., when worn as shoes or trousers. The fallacy of the test was pointed out by Siegel and Meltzer [2] in these words: "While patch tests give a fairly accurate idea of the relative cutaneous irritating and sensitizing properties of a new formula placed on the market, they do not always give an accurate idea of what may happen under conditions of actual use."


1,028 SUBJECTS WITH POSITIVE REACTIONS ON FIRST APPLICATION
598
430 SUBJECTS WITH POSITIVE REACTIONS ON BOTH APPLICATIONS
790
1,220 SUBJECTS WITH POSITIVE REACTIONS ON SECOND APPLICATION

Presentation of figures in table 1 to illustrate percentage of turnover in group of subjects exhibiting positive reactions to patch test.

We concur in the opinion expressed by Schwartz, Tulipan and Peck [1] to the effect that the potency of a material as a sensitizer should especially be reckoned with in determination of its acceptability for uses involving contact with the skin. However, the figures cited in this paper would seem to indicate that the accuracy of patch testing in assessing this property is not as great as these authors indicated when they wrote,[1] "Experience has shown that even one positive reaction among the second series (second application of the test patch) may indicate that the test substance is a sensitizer which might lead to outbreaks of dermatitis if allowed to be used by large groups of people." Figures are cited (table 1 and figure) which indicate that a reaction on second application of the test patch does not necessarily signify sensitization even when it follows a failure to react on first application. Our results show further that sensitization cannot be detected with much

2. Siegel, J. M., and Meltzer, L.: Patch Tests Versus Usage Tests with Special Reference to Volatile Ingredients, Arch. Dermat. & Syph. **57**:660-663 (April) 1948.

accuracy from the character of the reaction occurring on second application or from the sequence of reactions. It appears that one cannot say with any assurance that a vesicular reaction, for instance, signifies sensitization while a simple erythema or erythema plus edema does not. Nor have we found that the time of appearance or the duration of a reaction differs consistently in primary irritation and sensitization. To be certain on these points, one would have to correlate the patch test results with the experiences of thousands of persons on using or wearing the tested items.

Many factors interplay to determine the nature and extent of a subject's reaction to a material. Four are mentioned by Schwartz, Tulipan and Peck,[1] namely, "(1) The sensitivity of the patient, (2) the concentration of the substance used for patch testing, (3) the length of time it is permitted to remain on the skin, and (4) the amount of the substance per area of skin." The last three of these can be fairly well

TABLE 1.—*Summary of Results of Use of Schwartz Patch in Prophetic Patch Test Projects 1 to 14, with Exception of Projects 10 A and 11 and Patch 7 of Project 10* *

	Total	Reaction Positive on Second Application	Reaction Not Positive on Second Application
Reaction positive on first application	1,028	430	598
Reaction not positive on first application	8,346	790	7,556
Total	9,374	1,220	8,154

* Subjects included in this table are those who received the first application of the test patches and at least one reading and who also received the second application and at least one reading.

standardized and we have tried to make them so, following the technic and timetable previously described. The first of these factors may be said to include several "host" factors, such as the integrity, health, texture, thickness, vascularity, pigmentation, hairiness and sweating of the subject's skin, possibly his metabolic rate and endocrine state, the general state of his health, his habits of skin hygiene and his sensitivity or potential or actual allergy to the test substances. However, reactions do not always conform to predictions.

Individuals differ decidedly with respect to these host factors, but it is believed that a group as large as 300 civilian volunteers should be sufficiently like the personnel of the armed forces with respect to these factors to yield results applicable to that personnel.

There are, however, the following additional factors which influence a subject's reaction to a patch but for which it is more difficult to make satisfactory allowances than for the aforementioned factors: (1) the temperatures and humidities prevailing during the entire time the test patch is worn; (2) the amount of sweating underneath or moisture

coming from without into contact with the patch, determined by such things as the weather and working conditions; (3) the presence of various types of soil, dirt or grease, on the skin; (4) the intimacy of contact between the test patch and the skin, which is determined by the snugness of the overlying adhesive patch or band, the number and stiffness of hairs on the subject's skin and the firmness of the subject's tissues at the test site, the activity of the underlying muscles and the thickness, pliability, and shape of the patch; (5) the amount of friction between the test patch and the skin, and (6) the aeration of the

TABLE 2.—*Summary of Results of Use of Schwartz Patch in Prophetic Patch Testing of Shrink-Resistant and Untreated Woolen Flannels in August (Project 8)* *

	Total	Reaction Positive on Second Application	Reaction Not Positive on Second Application
Reaction positive on first application	113	56	57
Reaction not positive on first application	312	65	247
Total	425	121	304

* Subjects included in this table are those who received the first application of the test patches and at least one reading and who also received the second application and at least one reading.

TABLE 3.—*Summary of Results of Use of Schwartz Patch in Prophetic Patch Testing of Shrink-Resistant and Untreated Woolen Flannels in October (Project 9)* *

	Total	Reaction Positive on Second Application	Reaction Not Positive on Second Application
Reaction positive on first application	12	5	7
Reaction not positive on first application	581	12	569
Total	593	17	576

* Subjects included in this table are those who received the first application of the test patches and at least one reading and who also received the second application and at least one reading.

skin at the test site, which is a function of the porosity of the test patch and of the covering patch or band.

The same woolen flannel gave so many more reactions in hot weather than in cool weather (tables 2 and 3) that the results defied interpretation. In view of the differences in the microclimate under patches worn simultaneously by different persons, determined by the six factors mentioned, one wonders how much reliance one can place on patch tests performed during any season of the year.

The severity of the conditions surrounding the test, then, largely determines the proportion and severity of reactions, as is shown in tables 4 and 5 by results following the testing of various substances

simultaneously on the same subjects with test methods entailing different degrees of severity of contact. One procedure in prophetic patch testing, then, would be to make the conditions surrounding the test approximate as closely as possible the conditions which would surround the normal use of the item. Thus, the occlusive Schwartz patch would be selected for testing rubber for gas mask facepieces, while the porous arm band or the AIHL patch would be selected for testing woolen material for trousers. Another procedure, and one which the figures in tables 4 and 5 might be said to support, would be for one to use the severest test method, i. e., application of the "Schwartz" patch, for testing at all times, in order that some reactors could be counted on to appear in a

TABLE 4.—*A Comparison of the Proportion of Reactions Obtained on Prophetic Patch Testing with Mildew Proofed Leather, Untreated Leather, Shrink-Resistant Woolen Flannel and a Polyvinyl Chloride Film Simultaneously on the Same Subjects by Means of Two Different Test Methods*

Method of Testing	No. of Patches Applied and Followed by Readings	No. of Positive Reactions	Per Cent
Schwartz patch	2191	206	9
Arm band	2312	16	0.70

TABLE 5.—*Comparison of the Proportion of Reactions Obtained on Prophetic Patch Testing with Shrink-Resistant Woolen Flannel Simultaneously on the Same Subjects by Means of Three Different Test Methods*

Method of Testing	No. of Patches Applied and Followed by Readings	No. of Positive Reactions	Per Cent
Schwartz patch	258	22	8.5
AIHL patch	260	3	1
Arm band	260	0	0

group of 300 subjects, and to make allowances in the light of the normal use of the item in forming an opinion as to the item's acceptability.

The utility and reliability of the patch test in making the important determination of whether a substance is a primary irritant or a sensitizer are open to question in the light of the relation shown in the accompanying figure and the following statement by Siegel and Meltzer[2]: "A number of patients exhibiting so-called reactions of primary irritation in the first series did not show any reactions in the second. If a primary irritant is employed, the reactions of primary irritation should be reproducible." Likewise, it appears that if the reaction on first application is due to sensitization from past contact with the material, a reaction should be elicited on second application also.

The figures in table 1 indicate clearly that one cannot consider every second application reaction to indicate sensitization and suggest that one cannot even so consider every second application reaction which follows no reaction on the first application. The relations between the figures in this table suggest that through the use of statistical technics one could derive a more reliable index of sensitization from the number of reactions which is left over after the subtraction of the first application reactions from the second application reactions. We expect to go further and to derive, from statistical treatment of figures such as those in tables 6 and 7, a numerical value for each degree of severity of reaction and,

TABLE 6.—*Readings Made Twenty-Four Hours* After Removal of Patches in Prophetic Patch Testing in Projects 1 to 14 (with Exception of Projects 10 A and 11 and Patch 7 of Project 10), in Which the Schwartz Patch Was Used*

	0	?†	+	++	+++	Total
First application	8,572	110	679	22	6	9,389
Second application	8,526	37	784	36	6	9,389

* Only those subjects who had both first and second applications of test patches and whose reactions were read twenty-four hours or later after removal of patches figure in this table. When no reading was made at twenty-four hours the forty-eight hour reading is entered.

† These figures have little meaning, inasmuch as the practice of making forty-eight hour readings was discontinued after Project 5 (when only 2,406 of the 9,389 patches had been applied). Thereafter, only negative and positive entries were made for twenty-four hour readings.

TABLE 7.—*Readings Made Twenty-Four Hours* After Removal of Patches in "Prophetic" Patch Testing in Projects 10, 12 and 13, in Which the Arm Band Was Used*

	0	?	+	++	+++	Total
First application	2,983	0	44	1	0	3,028
Second application	2,959	0	67	2	0	3,028

* Only those subjects who had both first and second applications of test patches and whose reactions were read twenty-four hours or later after removal of patches figure in this table.

through the use of these values in further statistical computations, to assess more accurately the sensitizing potency of the item tested. A later report will deal with this matter. The relation in tables 1, 6 and 7, at any rate, incline us to the opinion that the reliability of second application reactions as an index of sensitization is much less than it is usually thought to be. Nor has the character of the reactions occurring on second application or the sequence of reactions proved to be a reliable index of sensitization in our experience.

In view of the role played by the microclimate at the test site in contributing to the severity of the reaction, and in line with the belief that the conditions surrounding the test of an item should approximate conditions surrounding the use of that item, a band of nonadhesive

elastic bandage was used experimentally for the testing of such items as fabrics for clothing. In bands made of inferior material three shortcomings are found which are not found in the Schwartz patch. These are a tendency to slip and cause the test patches to move about somewhat, a tendency to stretch and not maintain the test patches in sufficiently close or prolonged contact with the skin, and the production of difficulty for one in finding the exact spot covered by the test patches on the day following their removal. Moistening from perspiring or bathing increases the first two of these objectionable tendencies. These tendencies have been largely eliminated through instructions to the subjects and through the use of a better quality of material in making the bands. Experimentation is being conducted with the AIHL patch of elastic adhesive tape, which is of the same size as the Schwartz patch but without the cellophane backing and with a porous, adhesive-free circular area in the center under which the test patch is to lie.

The number of reactions from a given material tested under the band and AIHL patch has been only a fraction of the number of reactions from the same material tested on the same subjects simultaneously under the Schwartz patch (see tables 4 and 5). The difference has been so great that it is felt that further trial is indicated to establish the reliability of the band or AIHL patch even for the prophetic patch testing of items, such as trousers, which will have a degree of skin contact far less severe than, for instance, that of gas masks or hat sweatbands. Moreover, not only are there fewer reactions under the band or AIHL patch than under the Schwartz patch, but also the reactions are uniformly less severe, although the contact is generally close enough to leave on the skin an imprint of the test patch. This would seem to indicate that it would not be advisable to attribute significance only to reactions which reach a severity of 2 plus or greater under the band or AIHL patch, as we are inclined to do when using the Schwartz patch.

SUMMARY

The Army Industrial Hygiene Laboratory has made extensive use of the prophetic patch test. Results of the tests of certain items under the "Schwartz" patch under certain conditions have not accorded with other evidence at hand establishing the low order of irritancy of these items. This fact indicated that it might be worth while to make the intimacy and severity of contact between the item and the skin during testing approximate more closely the conditions expected during actual use. Thus we were led to the trial substitution for the Schwartz patch of a nonadhesive elastic band and of an elastic adhesive patch without the cellophane backing and with a circular, adhesive-free, porous center to hold the piece of test material in contact with the skin. Results with both new test methods warrant further trial.

The potency of an item as a sensitizer is conceded to merit greater weight than its potency as a primary irritant in the determination of its acceptability for uses involving contact with the skin. However, on the basis of patch test results alone we have not been able to make this differentiation with the desired assurance in the case of any substance tested. We have come not to give as great weight to reactions occurring on second application as most workers seem to give them. It is believed that through the application of statistical technic, due weight being given to reactions of varying degrees of severity and the first application reactions being discounted, a more reliable index of sensitization could be derived. Our results seem to indicate that when using the Schwartz patch one should (pending the aforementioned statistical refinements) attribute significance only to reactions of 2 plus or greater severity for purposes of determining the acceptability of an item. However, it appears that 1 plus reactions appearing under the AIHL patch or band are significant.

The definitive test of an item is provided by the use of that item for its intended purpose by sufficient numbers of persons over a sufficiently long period. Conditions in the military service make it impracticable and often impossible to accomplish this test, so that a rapid method of testing, such as the prophetic patch test, has to serve as the basis for judging an item. For this reason, it has been the purpose of those at this laboratory to discover the limitations of this test, overcome these limitations so far as possible and then take into account the inherent limitations of the test in judging each item tested, in order neither to accept unsafe items nor to reject safe and deserving items.

We believe that in proceeding along the lines discussed in this paper we have enhanced the utility and reliability of the prophetic patch test as a tool for use in determination of the acceptability from the toxicity standpoint of those items of military supplies and equipment destined for contact with the skin of personnel of the armed forces. We further believe that the Schwartz patch, the AIHL patch and the band all have their place in the patch testing program which those at the Army Industrial Hygiene Laboratory are called on to perform. It is confidently expected that the use of those items which have been judged on the basis of patch tests will substantiate these beliefs.

Drs. Robert H. Duguid, Ivan C. Tiholiz and Adelbert L. Stagg and Capt. Lee B. Grant, present and former medical officers of the Laboratory, assisted with the performance of the patch tests. Dr. Archie Blake and Mr. Arthur J. McDowell of the Medical Statistics Division of the Surgeon General's Office assisted in the statistical analysis and presentation of results of the patch testing. Capt. Kenneth S. Piggott, laboratory adjutant, handled the paper work connected with certain administrative and fiscal aspects of the patch testing. The Laboratory stenographers, Mrs. Julia M. Ewing, Mrs. Marietta M. Lancaster and Miss Mary Coyle, kept the records and derived the figures on the patch testing.

CHRONIC CUTANEOUS GRANULOMAS WITH SYSTEMIC INVOLVEMENT

A Report of Two Cases with Bacteriologic Studies

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IT IS THE intent of this paper to record the clinical findings and laboratory data, including the unusual bacteriologic findings, in 2 patients who had multiple cutaneous granulomas with systemic involvement. The disease phenomenon exhibited in these patients is unique in our experience and in that of others who have seen these patients.

REPORT OF CASES

CASE 1.—V. Z., a 12 year old white girl, was first seen by us on Jan. 26, 1945.

History.—She had had colds continually until the age of 10. She had had a tonsillectomy at the age of 7 and had had her "adenoids shrunk" on two occasions. She had had a vaginal discharge from infancy until five years before this illness. When 9 years old she had had an "infection" of the lungs, particularly the lower lobes. This infection had not been typical of pneumonia but had been thought to be a virus infection and had been accompanied by some pleural effusion. Immediately afterward the patient had had measles. She had lost 10 pounds (4.5 Kg.), and this was not regained. Thickening of the frontal bones had developed about July 1943. In the spring of 1944 the patient had had allergic rhinitis and had been found to be sensitive to several spring grasses. Her blood in September 1944 had shown a weakly positive Wassermann reaction. Wassermann, Kahn and Hinton tests of the blood of both parents had given negative reactions. Three subsequent blood specimens from the patient revealed negative reactions to Wassermann, Kahn and Hinton tests. The patient had had four injections of a bismuth preparation before we saw her. In October 1944 a nodular lesion had appeared on the posterior surface of her right thigh. It was excised. The pathologist's report on this tissue was that it was "nonspecific granuloma." Enlargement of the nasal bones developed shortly after the frontal bones had thickened. The patient had been given iodides, with some apparent decrease in enlargement of frontal and nasal bones but had acquired a generalized rash from the iodides which persisted on the arms and legs until the time of our examination although administration of the drug had been discontinued for several months.

Physical Examination.—On original examination the patient presented pronounced enlargement of the frontal bones and of the nose. The skin over these areas was dusky red and was involved in a noduloulcerative process with some

Read at the Sixty-Ninth Annual Meeting of the American Dermatological Association, Inc., at Hot Springs, Va., May 26, 1949.

tendency to central clearing (fig. 1). There were two quarter-sized noduloulcerative lesions with central atrophy on the vertex. There was a scar on the right thigh at the site of excision of the nodule. A red papular rash covered the flexor surfaces of the forearms and the legs. The remainder of observations on physical examination were not remarkable.

Laboratory Data.—Roentgenologic examination of the chest showed normal conditions except for a healed Gohn complex and possible enlargement of a right bronchial node. Roentgenologic diagnosis was "primary tuberculous infection, grade 1, healed." Roentgenologic examination of the skull revealed osteomyelitis of the frontal bones. Kolmer, Kahn, Hinton and Kline tests of the patient's blood gave negative reactions. The white blood cell count varied from 14,000 to 22,000.

Fig. 1 (case 1).—Noduloulcerative lesions involving the nose, cheeks and upper lip.

The differential ratio revealed 70 to 79 per cent polymorphonuclear leukocytes and 2 to 8 per cent eosinophils. Reexamination of sections of the lesion removed from the right thigh showed the histologic picture of a nonspecific granuloma. Biopsy of a nodular lesion on the forehead was reported by Dr. Hamilton Montgomery as showing a nonspecific granuloma with observations suggestive of a hematogenous type of tuberculosis. "Some sections showed an increase in plasma cells, but the picture was not that of a syphilitic process. No xanthoma cells of any type were seen. There were some collections of epithelioid cells suggestive of an atypical hematogenous type of tuberculosis. One of the sections showed deposition of hemosiderin but without any epithelioid cells or histiocytes. There was no evidence of any mycoses."

Treatment and Course.—For two months the treatment consisted in the application of promin® (sodium p,p′ diaminodiphenylsulfone-N,N′-didextrose sulfonate) ointment topically and filtered roentgen radiation to the involved areas of the forehead and nose. These sites improved. The hair fell out of the anterior 2 inches (5 cm.) of the scalp. The nodular and infiltrative process over the nose practically disappeared. During this time new nodules which ulcerated appeared on the hard palate and in the nares. A noduloulcerative lesion appeared on the right thigh.

Fig. 2 (case 1).—Typical noduloulcerative lesion on right leg.

About ninety days later new noduloulcerative lesions appeared on the cheeks, nose and arms. The new lesions appeared first either as subcutaneous or as cutaneous tender nodules. The skin over these lesions became red to purple. The lesions became centrally ulcerated and spread peripherally. A thick purulent exudate which was frequently bloody was discharged from the ulcerated centers (fig. 2).

The patient was referred to the Mayo Clinic. A summary of the report from there follows: "V. Z. was under our care from October 1945 to April 1946.

Results of urinalysis were normal on repeated occasions. The hemoglobin was around 11 to 12 Gm.; one reading in January 1946 was 9.8 Gm. The red cell count was 3,500,000 to 4,560,000, and the white cell count, from 10,000 to 16,000. The differential count showed eosinophils, 2 to 4 per cent; otherwise it was normal. Kolmer, Kahn, Hinton and Kline tests gave negative reactions. A roentgenogram of the chest on the first examination showed widening of the upper mediastinum. Later, in April 1946, roentgenologic examination revealed a pulmonary abscess of the upper lobe of the right lung, with cavitation. Roentgenograms of the skull showed osteomyelitis of the frontal bones. The patient acquired an acute infection in the right lung which responded to penicillin. Serum protein was 8.5 Gm. per hundred cubic centimeters, and the albumin-globulin ratio was 1.08:1.0. The sedimentation rate varied from 66 to 103 mm. The results of a dye excretion test for hepatic function were negative. Blood calcium and phosphorus during the administration of calciferol were normal. The Mantoux test and a test with purified protein derivative, both strengths, gave negative results on two occasions. Urine was negative for tubercle bacilli. Culture of the mouth showed a green-producing streptococcus. Results of guinea pig inoculation were negative. A histoplasmin skin test gave positive reactions, but we could not find the organism. Treatment was by supportive means, transfusions, large doses of vitamin D_2 and also streptomycin, 150,000,000 units. Among other considerations, we brought up the question of sarcoid, especially with involvement of the larynx, but we could not prove this diagnostic suggestion."

The patient remained at home under observation of her pediatrician, Dr. Lloyd K. Felter, from April 1946 to August 1946. Her condition became progressively worse, and finally she required a tracheotomy because of involvement of the larynx with obstructive phenomena. On her return examination on August 8, 1946, the cutaneous lesions on the frontal areas were found to have completely healed, leaving scars on which the hair had partially returned. The enlargement of the frontal bones had lessened considerably. The nose was flat and soft, as though the cartilaginous elements were absent. An ulcerative granulomatous process occupied the inner surfaces of the nasal passages. The cheeks had thickened. The left cheek showed several erythematous nodules. A noduloulcerative lesion with a purplish red infiltrated halo occupied the flush area of the right cheek. This ulcer was 3 inches (8 cm.) in diameter, irregular in outline and shallow. The base was covered by serosanguinous exudate and crusts. The hard palate showed a perforation 3 cm. in diameter. The tongue and upper lip were thickened and superficially ulcerated. A serosanguinous discharge exuded from the nose. A tracheotomy tube was in place. On the right thigh there was an infiltrated saucer-sized plaque which was erythematous and nodular. Her weight was 79 pounds (35.8 Kg.).

Her course was progressively downhill, with continued destruction of nasal structures, palate, pharynx, larynx and upper lip, until finally the right orbit became involved and the whole center of the face was a single, large, ulcerated, discharging mass. Multiple subcutaneous nodules, which later ulcerated, appeared on the trunk, scalp and extremities. These ulcers remained as open discharging, spreading lesions. The right knee became enlarged and tender, was limited in motion and had fluid. The right third toe became enlarged, red and ulcerated. A roentgenogram of the foot showed destruction of bone in this toe but no other bone lesions. The patient experienced repeated febrile episodes associated with fluid in the chest.

The serologic picture of the blood repeatedly showed normal conditions. The sputum was repeatedly negative for tubercle bacilli. Numerous specimens of fluid from the chest and the right knee were negative for tubercle bacilli as determined

by direct examination, culture and guinea pig inoculation. The sedimentation rate remained high, 70 to 100 mm. Repeated examinations of material from the cutaneous lesions revealed no fungi or amebas.

She was given several large courses of penicillin by injection and by inhalation, including one course of 6,000,000 units daily for sixty days. The penicillin seemed to help control the pathologic picture in the chest but did not influence the other lesions. Many agents, including sulfonamides, promin,® calcium and zinc peroxide, penicillin and bacitracin, were applied topically. Bacitracin and promin® were the only topical agents employed that seemed somewhat beneficial. The lesions treated with these chemicals slowly became clean granulating wounds. Some lesions healed, leaving depressed scars. Liver, vitamins, proteins and supportive measures were given.

The hemoglobin dropped to 50 per cent, and the red blood cell count, to 2,600,000, and the patient was given numerous transfusions. She acquired large, spreading ulcerations exposing the bones of the right shoulder, the left elbow and the skull. The nose, upper lip and right lower eyelid sloughed away. The entire center of the face became a large discharging cavity. The patient became weaker and more febrile and finally died on July 9, 1947. Permission for autopsy was not obtained.

Histologic Studies.—Two biopsies showed chronic granulomatous inflammation consisting of localized granulomas made up largely of epithelioid cells with scattered lymphocytes and eosinophils. The lesions exposed to secondary infection contained many polymorphonuclear cells. Giant cells were numerous. There was no caseation necrosis. Most of the lesions were related to small blood vessels, and in the surrounding tissues there was a perivascular lymphocytic infiltrate. The epidermis showed little or no alteration (fig. 3). Stains for acid-fast organisms revealed none.

Bacteriologic Studies.—On May 16, 1947, two "cold," subcutaneous abscesses, one of the scalp and one of the forehead, were carefully aspirated under aseptic conditions with the use of a syringe and needle. The skin over the abscess on the scalp was indurated but intact with no evidence of ulceration. The skin over the abscess on the forehead was indurated and centrally ulcerated. The aspiration yielded respectively 1.0 and 1.5 cc. of thick, grayish white, creamy and odorless pus. The aspirated material from each lesion was placed immediately into tubes containing cooked meat mediums, milk or blood agar, after which step these tubes were incubated aerobically and anaerobically for ten days at 37.5 C. Blood agar plates were inoculated with material obtained from the original cultures at intervals of two days during the first ten days, and these were incubated under aerobic and anaerobic conditions at 37.5 C. for seventy-two hours. A small nonsporulating, microaerophilic, gram-positive, non-acid-fast bacillus was obtained in pure culture from the scalp abscess. When first isolated the bacillus stained with great difficulty and was visible only in preparations stained with eosin. After subcultivation it was easily stained by the Gram method. This organism grew out slowly and was a nonmotile, short rod which did not ferment glucose, sucrose, maltose, levulose, mannose or xylose. Gelatin was not liquefied, and milk was not coagulated or digested by the growth of this bacterium. Indole was not produced, and tests for hydrogen sulfide elicited negative results. Nitrates were not reduced to nitrites. Attempts to identify the organism were unsuccessful.

From the abscess of the forehead, the same nonsporulating, microaerophilic, gram-positive bacillus was obtained, along with Escherichia coli, a coagulase-positive, nonhemolytic Staphylococcus aureus and a coagulase-positive, nonhemolytic Staphylococcus albus. The presence of the latter three organisms was undoubtedly the result of contamination of this lesion through the ulcerated surface.

Tests of sensitivity of the various bacteria to the available antibiotic agents were done. The microaerophilic gram-positive bacillus was found to be resistant to penicillin and sensitive to bacitracin and streptomycin. Both strains of staphylo-

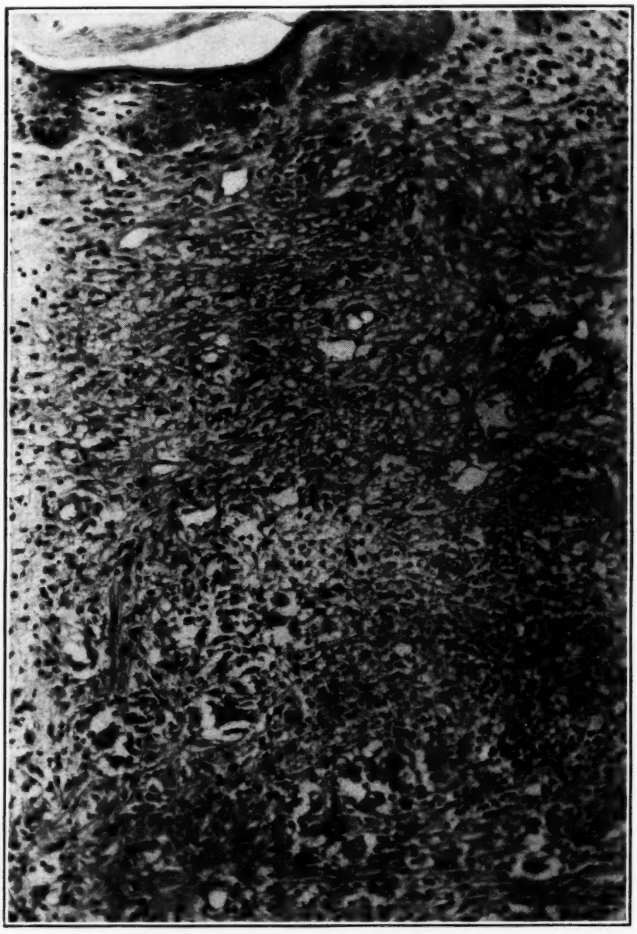

Fig. 3 (case 1).—Biopsy specimen taken from a lesion on the right arm showing localized granuloma made up largely of epithelioid cells with scattered lymphocytes and eosinophils and numerous giant cells. The perivascular lymphocytic infiltrate, lack of caseation necrosis and little change in the epidermis may be noted.

cocci were resistant to penicillin and sensitive to bacitracin. E. coli was found to be resistant to penicillin and bacitracin but sensitive to streptomycin.

Guinea pigs and mice were given injections intraperitoneally and subcutaneously with 0.5 cc., 1.0 cc. and 2.0 cc. of seventy-two hour cultures of the

microaerophilic gram-positive bacillus. Although these animals were observed for two months, no area of induration, ulceration or abscess formation developed at the point of subcutaneous injection, and a fatal peritonitis was not produced in any instance. Autopsies on these animals failed to reveal the presence of any enlarged lymph nodes.

CASE 2.—A. B., a 30 year old white woman, was first seen by us on June 9, 1944.

History.—She had had poliomyelitis which had affected the legs, arms and chest at the age of 9 years. There was residual paralysis of both legs. She had had surgical fusion of the right knee and partial fusion of both ankles. Since that time she had worn a brace on her left leg and walked with crutches. In 1935, she had had an infection following trauma to the surgical scar resulting from the operation to fuse the right knee. Two years were required for this infection to subside and the lesion to heal.

In 1937, she had had an infection in the left antecubital space at the site of insertion of a needle for a transfusion. This infection spread upward to involve the entire lower third of the anterior and lateral surfaces of the left upper arm. Since 1939, many full thickness grafts had been applied to this area. The areas on her back and on her right thigh from which donor grafts had been obtained had required two years to heal. She had had repeated episodes of fever and prostration lasting from several days to several weeks.

Physical Examination.—On original examination she presented an area on the left upper arm involving the anterior and lateral surfaces extending from the antecubital space 4 inches (10 cm.) up the arm. The center of this area was covered by several skin grafts each about 1 inch (2.5 cm.) square. There was an infiltrated ulcer at the top, and one at the bottom, of the grafted area. The denuded area in the upper ulcer was ½ inch (1.2 cm.), and in the lower, 1 inch in diameter (fig. 4). The periphery of each of these ulcers was elevated, bluish and hard. Each base appeared glazed and discharged a thin serosanguinous fluid. The remainder of the observations on physical examination other than the paresis, fused joints and scars already mentioned were not remarkable except for some impairment of breath sounds in the left upper portion of the thorax.

Treatment and Course of Patient While Ambulatory.—Compresses of tyrothricin were applied, and in two months the ulcers had lost their borders of induration and the bases were covered with healthy-appearing granulation tissue. Four attempts were made to place grafts at these sites with skin from the right thigh. The grafts failed to take; the donor sites on the thigh failed to heal and became granulomatous and ulcerated (fig. 5). A chronic ulcerated granuloma appeared after trauma on the lateral surface of the right ankle just above the external malleolus. Subsequent treatment consisted in the application of many types of topical agents such as sulfonamides, penicillin, streptomycin, tyrothricin, gliotoxin, oxyquinoline sulfate, preparations of mercury, chlorophyll compounds, urea peroxide, calcium and zinc peroxide and bismuth tribromophenate (xeroform®). Internally penicillin and sulfonamides were administered repeatedly for febrile episodes associated with cough and expectoration during the four years she was observed as an ambulatory patient.

In 1946, a diagnosis of pulmonary tuberculosis was made on roentgenologic findings only. Some 300 specimens of sputum were negative for tubercle bacilli. In early childhood the patient had had transient contact with an aunt and uncle who died of tuberculosis. Therapeutic sterilization with roentgen irradiation was done in 1946. The patient was hospitalized on April 26, 1948, and has been at bed rest since that date.

Laboratory Data.—A roentgenogram of the chest revealed the bony framework, heart, diaphragm and midline structures to be within normal limits. The left upper pulmonary field and apex showed parenchymal scarring and thickening of the pleura, and there were increased markings from the left hilus to this area. The remaining pulmonary fields revealed essentially normal conditions. Roentgenograms taken on May 17, July 26, Sept. 27, Oct. 14 and Nov. 16, 1948, and Jan. 12, 1949, were exactly the same. Roentgenograms taken elsewhere two and five years earlier

Fig. 4 (case 2).—Noduloulcerative lesion on the left arm.

revealed exactly the same pathologic picture. Roentgenograms of the teeth, gall bladder and gastrointestinal tract showed normal conditions. The basal metabolic rate was + 20. The results of many urinalyses were normal. Blood sugar, urea, urea nitrogen, nonprotein nitrogen, the albumin-globulin ratio and total protein were within normal limits. Several cultures of the blood were sterile. The serologic picture of the blood was within normal limits. The sputum on 157 examinations was negative for tubercle bacilli. Gastric washings were negative for tubercle bacilli. The stool was negative for tubercle bacilli and for ova and parasites.

Agglutination tests of the blood for typhoid, paratyphoid, dysentery, undulant fever and tularemia gave negative reactions. Tuberculin tests gave negative reactions. The reaction in the intradermal test with histoplasmin was weakly positive, but the organism could not be found. The white blood cell count varied from 5,600 to 2,200. The differential count was not remarkable except for observation of 3 to 4 per cent eosinophils and the occasional appearance of a few mast cells. The hemoglobin varied from 10 to 11 Gm. The red cell count was 3,200,000 to 4,100,000. Tests of guinea pigs inoculated with sputum and material aspirated by bronchoscopy were negative repeatedly for tuberculosis. Cultures and direct examinations of material from the cutaneous lesions and sputum were negative for fungi, yeasts and amebas. The lesions on the left arm and right thigh were completely excised and the material studied histologically and bacteriologically. The surgical wounds failed to heal and became ulcerated granulomas.

Treatment and Course in Hospital.—Her course in the hospital has been steadily downhill. She has maintained a constant elevation of temperature, with temperatures varying between 100 and 104 F. Her weight has slowly diminished from 108 pounds (49 Kg.) to 72 pounds (33 Kg.). The white cell count has varied from

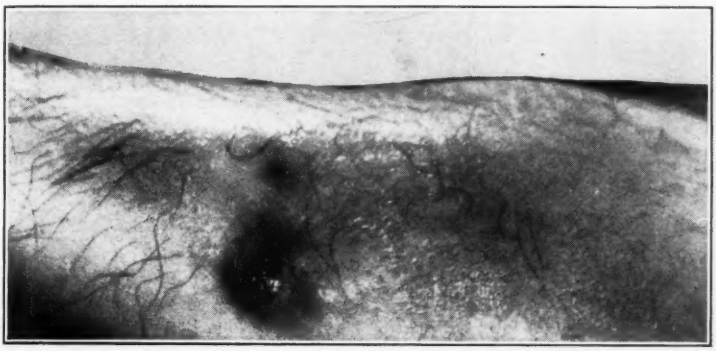

Fig. 5 (case 2).—Noduloulcerative lesion on the right thigh.

2,600 to 4,800; the hemoglobin, from 9.8 to 11.5 mg., and the red cell count, from 2,900,000 to 4,000,000.

The lesion on the right ankle healed completely in six months, leaving a hyperpigmented thin scar. In eleven months the wounds resulting from excision of the granulomas on the left arm and right thigh have slowly receded with the topical use of bacitracin, chlorophyll and carotene ointments. Only small, 0.5 cm. areas are still not epithelized. A high calory and high vitamin diet has been maintained. The patient was given transfusions to which she became increasingly reactive until they were finally discontinued. Streptomycin, 1 Gm. daily, was administered parenterally for one month. Its use had to be discontinued because of tinnitus, which cleared after discontinuance of the drug. The patient seemed generally improved while taking it. Bacitracin was given intramuscularly but had to be discontinued after one week because of renal toxicity. Albumin disappeared from the urine shortly after withdrawal of the bacitracin.

Four million units of penicillin were given daily for thirty days without benefit. Iodides given orally, 150 to 200 grains daily for ninety days, did not influence the disease. The administration of estrogenic substances, lextron® (liver-stomach

concentrate with iron and the vitamin B complex) with ferrous gluconate and vitamins, including calciferol, were not beneficial. Calcium pantothenate (2,000 mg. daily) was given for months without apparent change. Autogenous vaccine (contents described below), though detoxified and very dilute, produced pronounced febrile and systemic toxic reactions on each injection. Control injections of comparable amounts of colon bacillus vaccine and a vaccine composed of several strains of streptococci and staphylococci together with three strains of Micrococcus catarrhalis failed to produce reactions of any type.

Histologic Studies.—On May 5, 1948, a biopsy specimen from the ulcerated lesion on the left arm showed no remarkable change in the stratified squamous

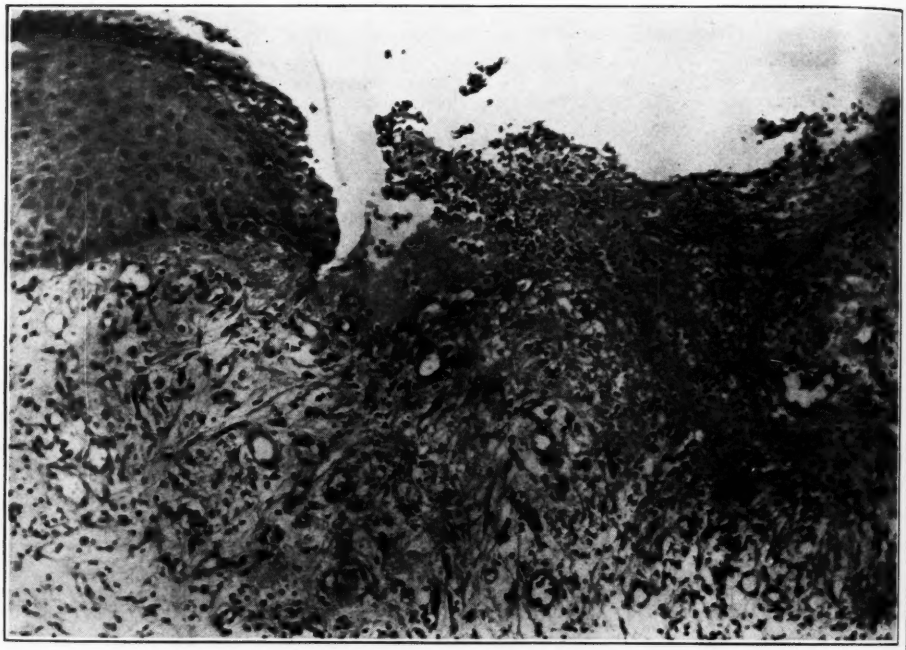

Fig. 6 (case 2).—Biopsy specimen taken from a lesion on the right arm showing little change in the epidermis except that it is denuded from part of the specimen. Underlying and adjacent to the denuded area is a dense connective tissue stroma diffusely infiltrated with epithelioid cells, lymphocytes, eosinophils, numerous giant cells and a few plasma cells. There is no caseation necrosis or xanthoma cells.

epithelium except that it was denuded from part of the specimen. Underlying this denuded area and adjacent to it there was a dense connective tissue stroma which was diffusely infiltrated with epithelioid cells, lymphocytes, plasma cells and eosinophils (fig. 6). There was no tubercle formation or caseation necrosis. There were no xanthoma cells and no evidence of any mycoses. On July 8, 1948, a biopsy specimen from the granuloma on the right thigh showed exactly the same histologic picture as did the specimen from the arm except that fewer plasma cells were seen. Numerous giant cells were present in each specimen studied.

Bacteriologic Studies.—Cultures in cooked meat medium were made on three occasions, from biopsy specimens from the ulcerating lesions of the left arm and the right thigh and from sputum specimens. A microaerophilic, gram-positive, nonsporulating, nonmotile bacillus was isolated from the material from all three sources. In the original cultures it failed to stain by the Gram method but did stain with eosin. Organisms from subcultures stained easily by the Gram method. When subcultures were grown on blood agar plates, small, smooth, white colonies were produced. This organism grew out slowly and was a nonmotile, short rod, which did not ferment glucose, sucrose, maltose, levulose, mannose or xylose. Gelatin was not liquefied and milk was not coagulated or digested by the growth of this bacterium. Indole was not produced, and tests for hydrogen sulfide were negative. Nitrates were not reduced to nitrites. Attempts to identify the organism were unsuccessful. It was found to be susceptible to penicillin, bacitracin and streptomycin but resistant to aureomycin, chloramphenicol (chloromycetin®) and polymixin B.

An anaerobic, gram-variable bacillus which was nonsporulating and nonmotile was also isolated. Attempts to identify it were likewise unsuccessful. It was found to be susceptible to bacitracin and streptomycin but resistant to penicillin, aureomycin, chloramphenicol and polymixin B. These two organisms, the microaerophilic, gram-positive bacillus and the anaerobic, gram-variable bacillus, were found in each of the three specimens cultured. From the ulcerating lesion on the arm, a hemolytic Staph. aureus which was coagulase-positive was also isolated. This organism was susceptible to streptomycin and bacitracin but resistant to penicillin. E. coli and a diphtheroid were also found in the sputum.

Guinea pigs were then given subcutaneous and intraperitoneal injections of 0.5 cc. of the microaerophilic, nonsporulating, gram-positive bacillus culture. One of the animals died seven days after the injection, and the others survived. Autopsy showed the presence of biliary peritonitis and enlargement of the liver. Cultures taken of the fluid in the peritoneal cavity at autopsy showed a variety of intestinal organisms, but the microaerophilic bacillus was not recovered. Two more guinea pigs were given injections of 1.0 cc. of the culture of the microaerophilic, nonsporulating, gram-positive bacillus, and again one pig died. Autopsy again showed the presence of jaundice, enlargement of the liver and early lobar pneumonia. The microaerophilic, gram-positive bacillus was not recovered on culture of the fluid in the peritoneal cavity. Four guinea pigs were given injections of 0.5 cc. and four, injections of 1.0 cc. of cultures of the anaerobic, nonsporulating, gram-variable bacillus. No signs of pathogenicity of this organism were elicited.

Four mice were likewise given injections of 0.5 cc. and four, injections of 1.0 cc. of cultures of the microaerophilic, gram-positive bacillus. These animals were kept six months, and no evidence of pathogenicity was found. Four mice were given injections of 0.5 cc. and four, injections of 1.0 cc. of cultures of the anaerobic, gram-variable bacillus, and again no evidence of pathogenicity was elicited; all animals survived six months.

The patient's skin was tested on July 3, 1948, with heat-killed suspensions of the microaerophilic, gram-positive bacillus; the anaerobic, nonsporulating, gram-variable bacillus, and the hemolytic Staph. aureus. She showed the following reaction in twenty-four hours: an erythematous, elevated area measuring 3 inches (8 cm.) in diameter as a reaction to the microaerophilic, gram-positive bacillus; a similar area 4 inches in diameter as a reaction to the anaerobic, nonsporulating, gram-variable bacillus, and a negative reaction to the hemolytic Staph. aureus. A vaccine composed of equal parts of the microaerophilic, gram-positive bacillus and the anaerobic, gram-variable bacillus was prepared for therapeutic trial.

COMMENTS

The presumption of a common etiologic factor for the disease phenomena exhibited would seem reasonable, in view of the relatively similar clinical findings of cutaneous granulomas with systemic involvement and the chronic clinical decline in these 2 patients. The similar histologic observations of a nonspecific type of inflammatory process in the granulomas of the patients could also be explained by some common provoking agent. All attempts failed to demonstrate a known etiologic agent such as the tubercle bacillus, Treponema pallidum, the mycoses or the established pathogenic bacteria. It was impossible to prove the presence of sarcoid in either patient.

The finding of a nonsporulating, nonmotile, microaerophilic, gram-positive bacillus in each specimen of material studied from each of these 2 patients seemed significant. The slow growth and peculiar staining characteristics of this organism could easily account for the unsuccessful attempts to obtain it from each of these patients in earlier studies here and elsewhere.

The microaerophilic, gram-positive bacillus was isolated, and the tests of sensitivity to the various antibiotics were done, after each patient had had many courses of penicillin. In the first patient, the apparent control of the pulmonary and joint episodes by penicillin may indicate that the organism was originally susceptible to penicillin but became resistant by the time our tests were done. In the second patient the apparent control of the acute, febrile, pulmonary episodes by penicillin may be due to the fact that in the highly vascular pulmonary tissue the penicillin reached the organism in sufficient concentration to destroy it. The failure of penicillin to influence the granulomas may be explained on the basis that in these dense cellular areas the organism was not reached by the penicillin in lethal concentration. The failure of streptomycin to destroy the granulomas in both patients may be on the same basis. Both patients experienced some degree of general improvement while they were receiving streptomycin. Bacitracin for parenteral use was unavailable for administration to the first patient and its administration to the second patient had to be discontinued before adequate trial was obtained.

In the second patient, the decided local, febrile and toxic systemic symptoms provoked by intradermal injection of the vaccine containing the microaerophilic, gram-positive bacillus and the failure of such reactions to occur on injection of vaccines containing other organisms seemed to indicate some etiologic relation of this organism to the disease syndrome.

Certainly the observations recorded here should provoke search for similar organisms in future patients who have chronic cutaneous granulomas with systemic involvement. Additional search for an effective therapeutic approach will be continued.

ABSTRACT OF DISCUSSION

DR. J. GARDNER HOPKINS, New York: Dr. Welsh has presented 2 extraordinary and baffling cases. They do seem somewhat unlike.

The same possible etiologic factors probably occur to most of us, but the presenter and many consultants who have studied these cases for years have been unable to put them in any known category. It would be futile to attempt a diagnosis from descriptions.

Probably most of us have seen cases of chronic ulceration of which we could make no diagnosis. After hearing the present report, one hopes that Dr. Welsh has found the explanation. If so, he has described a new disease entity caused by a heretofore unknown bacillus—a contribution of the very first rank.

The author himself has laudably refrained from making any such claim, but, if subsequent observers are to attempt to identify their cultures with his, it seems necessary to know more details.

What was the size of these bacilli, and what was their shape? Were they ever club shaped or irregular? Did they form clumps or chains or perhaps even filaments? How did they react to metachromatic stains? To what extent was the one microaerophilic, and did it remain so? Were the fermentation tests done anaerobically? The failure to stain when first isolated seems remarkable. Did Dr. Welsh try treating the films with acetone? Such details seem important.

The description given of the first strain hardly excludes the smooth form of Actinomyces bovis or one of the wound anaerobes, but neither is known to produce such clinical pictures. The description does not exclude the diphtheroids. These are sometimes regular in outline and stain evenly with many dyes. Some are microaerophilic. Although most of them form acid from some sugars, Andrews and associates observed that of 79 strains isolated from throats, 18 did not ferment glucose or any other sugar tested.

If these bacteria are diphtheroids, one must remember that strains of this group have been isolated from closed lesions of many types. In the past, excellent observers have reported them as the cause of Hodgkin's disease, of typhus fever and of acne, only to find later that they bore no etiologic relation to the diseases in question.

This has been a most interesting presentation. It is important to record such studies for the aid of subsequent investigators. We shall all be on the lookout for similar cases, and, as a result of Dr. Welsh's observations, we shall study them with renewed interest and hope.

DR. JOHN F. MADDEN, St. Paul.: I am not sure that this is not a case of human necrobacillosis. The organism in necrobacillosis is a gram-negative anaerobe and I think that Dr. Welsh should, on his return, consult the veterinary department either at the University of Ohio or the University of Cincinnati and be sure that that disease is excluded. If that possibility remains, he might aid the patient by using the vaccine commonly employed by veterinarians for necrobacillosis in animals.

DR. FRED D. WEIDMAN, Philadelphia: My reaction was similar to that of Dr. Hopkins—that is, that on the face of it it appears that we have here a new clinical and etiologic entity, but that there are doubts whether the micro-organism is a new species. Unfortunately, but few departments of dermatology have a bacteriologic laboratory and the personnel to conduct exhaustive studies of bacteriologic problems like this, and consequently most must turn to the departments of bacteriology in medical schools. It is encouraging that our dermatology departments have done fairly well in studies of the fungi and that one or two of them have established facilities for research on the viruses, but it remains for them to correct the deficien-

cies in bacteriologic studies. Such remarkable strides have been made in bacteriology that but few dermatologists can keep up with the procession, and, if they make the attempt, it should become more or less a hobby, perhaps to the exclusion of work with the other fields of basic science investigation. In every dermatology department, some staff member should be designated as the bacteriologist and it should be expected of him that he become proficient in all the minutiae of the subject.

In granulomatous cases like Dr. Welsh's, the usual procedure is first to exclude tuberculosis, syphilis and the fungous infections. However, there remain cases in which one comes up against a stone wall and which one has to call "granulomas of undetermined nature." In the nature of things, some of these must be bacterial. In dermatology a few of them have been classified, and Dr. Welsh's description of his patient with destruction in the center of the face recalls Dennie's "Massive Necrosis of the Center of the Face," which was due to spirochetes in symbiosis with various bacterial species. Dr. Madden just mentioned Actinomyces necrophorus (Bacillus necrophorus), and actinobacillosis is an actinomycosis-like disease. Infection with Pseudomonas aeruginosa (Bacillus pyocyaneus) is another. Castellani has described granulomas caused by the typhoid bacillus and Bacillus pseudomyceticus, too. These are bacterial granulomatous diseases which I can think of on the spur of the moment, and it would not be amiss to construct a complete catalog as a beginning in the proper development of our knowledge of the bacterial granulomas.

Dr. Louis A. Brunsting, Rochester, Minn.: It takes a good deal of courage to give a paper of this type. Most of us shy away from clinical reports, as in the 2 cases here presented where the records of illness extend over a period of several years and the differential diagnosis is so comprehensive. The first patient was under my observation for a little more than one year. At one time the picture was that of sarcoidosis and the interpretation of the results of biopsy was more or less confirmatory; empiric treatment included large doses of vitamin D_2 and streptomycin and supportive measures such as the transfusion of blood. In spite of this there was a gradual progression of the granulomatous process to include extensive destruction of parts of the face and nasopharynx. I was struck by the lack of defense of the tissues against the invading process. I believe it will take further work to prove a significant relation between this disease and the organism that has been demonstrated.

Dr. Samuel Ayres Jr., Los Angeles: Did either of these cases begin with herpetic lesions which subsequently underwent granulomatous changes? My associates and I have seen 2 cases over the past three or four years in which that sequence seems to have developed.

Dr. Ashton L. Welsh, Cincinnati: As Dr. Brunsting has intimated, a great many of our negative findings were not mentioned. Neither patient had been out of this country.

A more detailed description of the organism, as Dr. Hopkins has suggested, is certainly in order. It will be included in a subsequent report. The organism had been injected into animals other than those mentioned, including hamsters. There are many more negative than positive findings. Herpetic lesions have not been observed to precede the granulomatous lesions. The ulcers began with palpable nodules beneath the skin. We are planning to continue every effort to identify the organism.

SPINDLE CELL EPIDERMOID CARCINOMA

Report of Five Cases in Patients Who Had Never Been Exposed to Roentgen Rays

MAURICE J. STRAUSS, M.D.
NEW HAVEN, CONN.

WITH THE publication by Sims and Kirsch [1] of a report of 2 cases of spindle cell epidermoid carcinoma, attention has again been called to this unusual and strange type of epithelioma. Sims and Kirsch also repeated the assertion of previous writers that this type of neoplasm occurs in epithelium damaged by chronic radiodermatitis and is probably the result of the previous exposure to roentgen rays. This is a report of 5 cases of such cancers occurring in patients who had never been exposed to roentgen rays or radium.

Spindle cell epidermoid carcinoma of the skin, of the type reported in this paper, was first reported in this country in 1935 by Martin and Stewart.[2] They reported in detail 8 cases, in 6 of which the patient had received roentgen ray therapy (5 of these persons showing clinical evidence of chronic radiodermatitis) and in 1 of which the patient had been treated with radium and had suffered a contused wound at the site of the tumor. Although Martin and Stewart conceded that there might be other causes of spindle cell epidermoid carcinoma, they expressed the opinion that roentgen therapy was the most important cause. They made this statement: "Undoubtedly the most common cause for the peculiar morphology of these tumors is roentgen irradiation. It is not the only cause."

Sims and Kirsch did not go into any lengthy discussion of the possible causes of spindle cell epidermoid carcinoma, but both of their patients had received roentgen ray therapy and showed evidence of chronic radiodermatitis. These authors expressed their theory of the etiology of these tumors as follows: "We call attention to another type of epidermoid epithelioma that occasionally occurs in patients with, and is probably caused by, chronic radiodermatitis."

From the Division of Dermatology of the Yale University School of Medicine.

Read before the Section on Dermatology and Syphilology at the Ninety-Eighth Annual Session of the American Medical Association, Atlantic City, N. J., June 9, 1949.

1. Sims, C. F., and Kirsch, N.: Spindle Cell Epidermoid Epithelioma Simulating Sarcoma in Chronic Radiodermatitis, Arch. Dermat. & Syph. **57**:63-68 (Jan.) 1948.

2. Martin, H. E., and Stewart, F. W.: Spindle-Cell Epidermoid Carcinoma, Am. J. Cancer **24**:273-298 (June) 1935.

In the cases reported here as well as in those of Martin and Stewart and Sims and Kirsch, a diagnosis of epithelioma was clearly suggested by the clinical appearance of the tumor. In 1935, Montgomery [3] also reported 2 cases of epithelioma simulating endothelioma, sarcoma and sporotrichosis. It is obvious from the title of his report and from the illustrations published that the patients presented a clinical picture which did not suggest a diagnosis of epithelioma. In fact, Montgomery's illustrations bear a decided resemblance to those in a paper cited by him. This was a report by Perkins [4] of a case of epithelioma of the hand which resembled endothelioma. There is no evidence in Perkins' report that any spindle cell formation was observed, but in both of Montgomery's patients the histopathologic picture was that of epithelioma simulating sarcoma. Montgomery stated that it was his opinion "that the majority of so-called endotheliomas or sarcomas of the extremities will prove, on careful histologic study of multiple or serial sections, to be squamous-cell epitheliomas." Both Martin and Stewart and Sims and Kirsch cited earlier reports of sarcomas occurring in radiodermatitis and suggested that these may have been carcinomas mistaken for sarcomas because of their unusual cellular structure.

I have seen 2 cases of spindle cell epidermoid carcinoma in patients who had not received any roentgen therapy. In addition, a search of the records of the patients at the New Haven Hospital with a confirmed diagnosis of epidermoid carcinoma of the skin brought to light 3 more cases of spindle cell carcinomas in patients who had never received radiation therapy. These 5 cases are reported here.

REPORT OF CASES

CASE 1.—M. S., a white woman aged 35, was first seen on May 29, 1944. She presented a tumor which had been slowly growing for about five years. The lesion was an oval infiltrated plaque with a scaly surface, located on the left upper arm just anterior to the anterior axillary fold. The color was a pale pink, and there was a crusted area in the center of the lesion. This crust was easily removed, leaving a raw, oozing surface. The serologic picture was normal. On June 2, 1944, the entire lesion was excised with the use of procaine hydrochloride (novocain®) anesthesia. A stitch abscess developed, delaying healing somewhat, but the wound was completely healed on July 28, 1944. There had been no evidence of recurrence when the patient was last seen, on Sept. 20, 1948. The patient had never received any roentgen ray therapy.

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3. Montgomery, H.: Epitheliomas of the Arm Simulating Endothelioma, Sarcoma, and Sporotrichosis: Two Unusual Cases, M. Clin. North America **19**:605-610 (Sept.) 1935.

4. Perkins, W. A.: Epithelioma of the Hand—A Study in Differential Diagnosis Between Epithelioma and Endothelioma, California & West. Med. **22**:448-450 (Sept.) 1924.

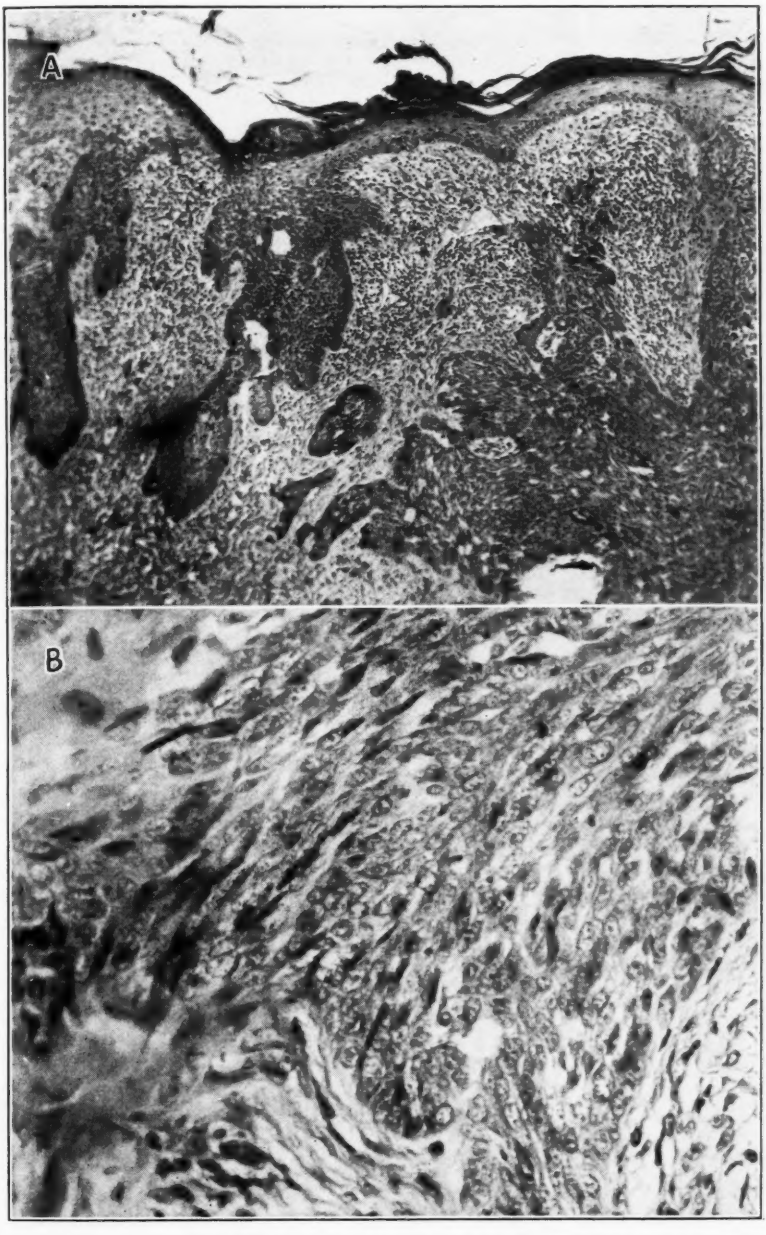

Fig. 1 (case 1).—*A*, showing the epidermal origin; × 85. *B*, showing spindle-shaped nuclei in spindle-shaped cells; × 440.

Histologic examination revealed the following picture. There were broad areas of epidermoid cells which resembled prickle cells with numerous mitotic figures. In some areas the tumor cells had assumed a definite spindle shape and were packed very closely. These masses of tumor cells had a well preserved basement membrane except for a few narrow places where the tumor infiltrated diffusely into the surrounding tissue. The epidermis over this was mostly necrotic; toward the periphery it was papillary and hyperkeratotic. The rete pegs were elongated and fused with the tumor mass.

CASE 2.—H. W., a 78 year old man, was seen first on April 23, 1945. He presented on the dorsal surface of both hands several dry, hard, crusted, keratotic lesions clinically typical of senile keratoses. On the extensor surface of the right wrist there was a verrucous, round, elevated nodule about 1 inch (2.5 cm.) in diameter, surrounded by a zone of erythema. This lesion bled freely on the slightest trauma. The patient had never had any radiation therapy. He had spent a good deal of time in the sun. On May 2, 1945, the lesion on the wrist was excised with the use of procaine anesthesia. The wound healed promptly, and there had been no evidence of recurrence when the patient died of cardiac failure two years later.

Microscopic examination showed that except for a small central area there was stratified squamous epithelium, with a heavy keratinized layer on the outside. Extending down into the corium were narrow columns, two or three cell layers thick, of pale-staining cells with vesicular nuclei, containing numerous mitotic figures. The cells tended to assume a spindle shape in some locations, and in these locations the nuclei were elongated and oval. Occasionally the columns themselves joined together to produce a sheet of such cells. There was a surrounding round cell infiltration.

CASE 3.—B. R., a white woman, had been a patient in the New Haven Hospital on several occasions with arteriosclerotic heart disease, auricular fibrillation and obesity. She was 47 years old when she first complained of a nodule at the lid margin of the right lower eyelid, which she said had been present for about one year. On examination there was seen at about the middle of the right lower lid a small lesion about 3 mm. in diameter. It was indurated, had a rolled edge and showed a central ulceration. On Nov. 8, 1944, a small piece was removed for microscopic examination and revealed the picture of spindle cell epidermoid carcinoma. The entire lesion was then excised on November 20 and was found to be a mixed basal cell and epidermoid tumor with many areas of spindle cell epidermoid cells. There was no history of any radiation therapy. In January 1945 there was apparent in the center of the scar a small, hard, freely movable nodule. By February this had attained a size of 6 mm. in diameter. It was excised and proved to be a foreign body reaction around a piece of black silk. On three more occasions during that year pieces of black silk were removed from the conjunctival surface of the lid. On Sept. 18, 1946, the patient returned with a tumor on the lateral portion of the left lower eyelid. This lesion was a heaped-up, indurated nodule about 4 mm. in diameter with a central crusted ulceration. This was excised and found to be an epidermoid carcinoma. When the patient was last seen, on June 14, 1948, there was no evidence of recurrence of either of these lesions.

The original biopsy specimen showed a wild growth of epithelial cells. The fibrous connective tissue was invaded and very thin and supported the cores of epithelial cells which grew deeply into it. The epithelial cells were spindle shaped and tended to grow in whorls. The nuclei were large and deep staining, and a small amount of pink cytoplasm was present. Scattered throughout this growth of epithelial cells were a few small, round, inflammatory lymphocytic cells. A few mitotic figures were present.

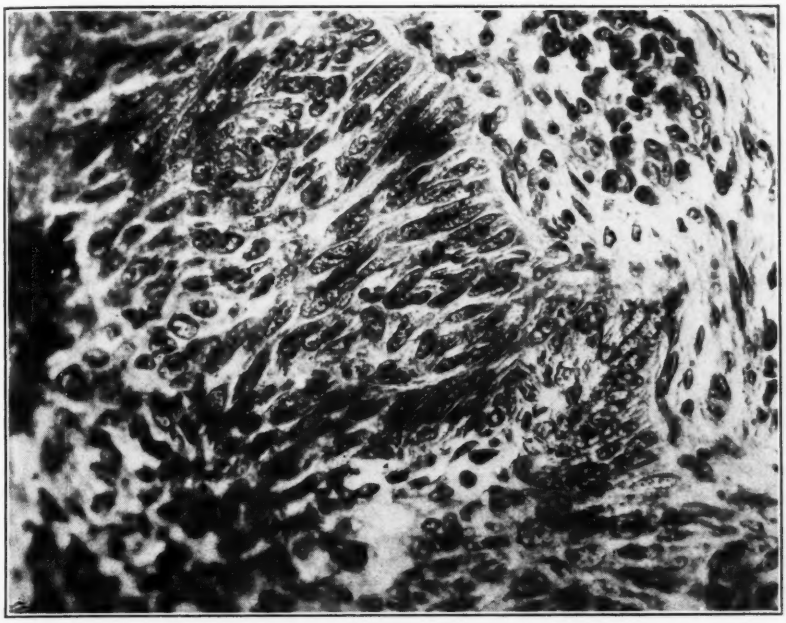

Fig. 2 (case 2).—Showing the parallel arrangement of the cells in some places; × 440.

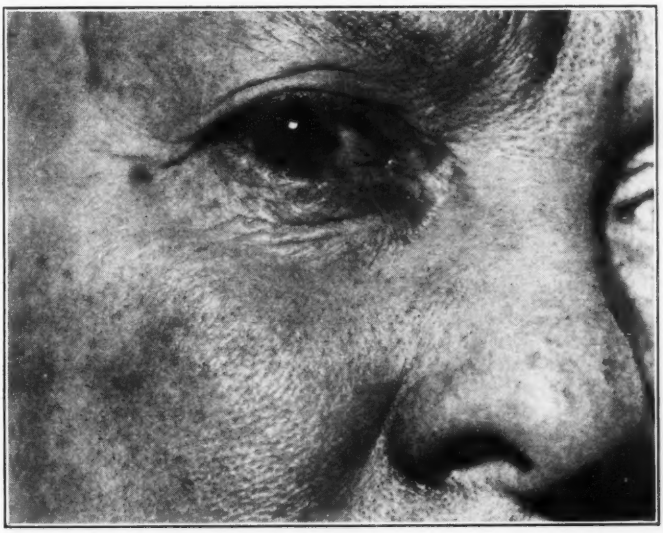

Fig. 3 (case 3).—The lesion itself is innocuous in appearance.

The section of the excised tumor showed a normal bit of stratified squamous epithelium with normal rete pegs. Following this along there were seen nests of epithelial cells which grew deep in the fibrous connective tissue stroma. These epithelial cells were similar to those which were found in the basal layer of the epithelium. Deeper in the section there were columns and bands of epidermoid cells intertwined in various directions. Some of these cells were polyhedral or oval with large oval nuclei, but the majority were spindle shaped with spindle-shaped nuclei.

CASE 4.—J. L., a 66 year old white man, was first seen in March 1948. He complained of a nodule on his lip of one year's duration. The lesion was a bean-sized nodule at the vermilion border of the lower lip. It was an indurated, ulcerated nodule, and the ulcer was covered with a thick crust. There was also a

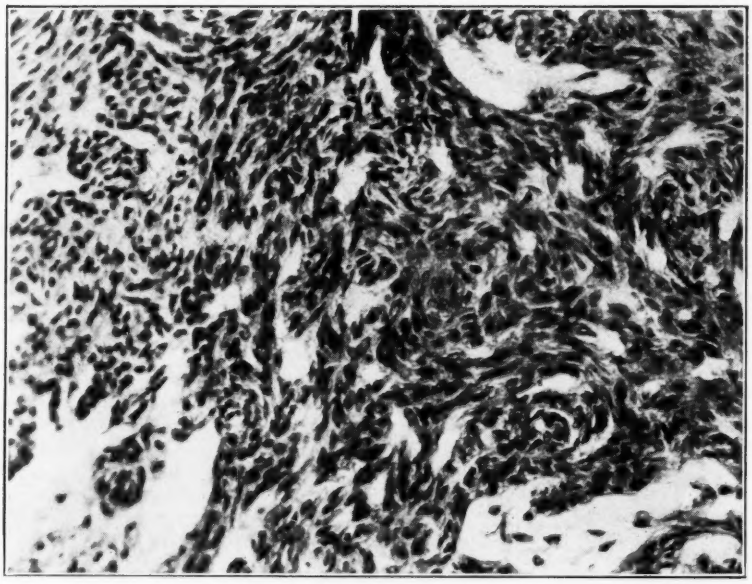

Fig. 4 (case 3).—Section from the biopsy specimen, showing the pronounced resemblance to sarcoma; × 440.

clinically typical seborrheic keratosis in the right temporal area, several dry keratotic areas on the dorsum of the hands and an elevated round lesion with a central ulceration about 15 mm. lateral to the right labial commissure. This nodule was about 6 mm. in diameter. On April 15, 1948, both the lesion on the lip and the one on the right cheek were excised. The lesion on the cheek showed the picture of a typical epidermoid carcinoma, while the one on the lip showed that of a spindle cell epidermoid carcinoma. The patient had never received any roentgen ray or radium therapy.

Microscopic examination of the tumor removed from the lip showed at one end of the section surrounding two hair follicles a cellular mass infiltrating deeply into the cutis. The cells were arranged in concentric whorl-like patterns. The nuclei were stained very lightly and had a vesicular chromatin network. The cytoplasm

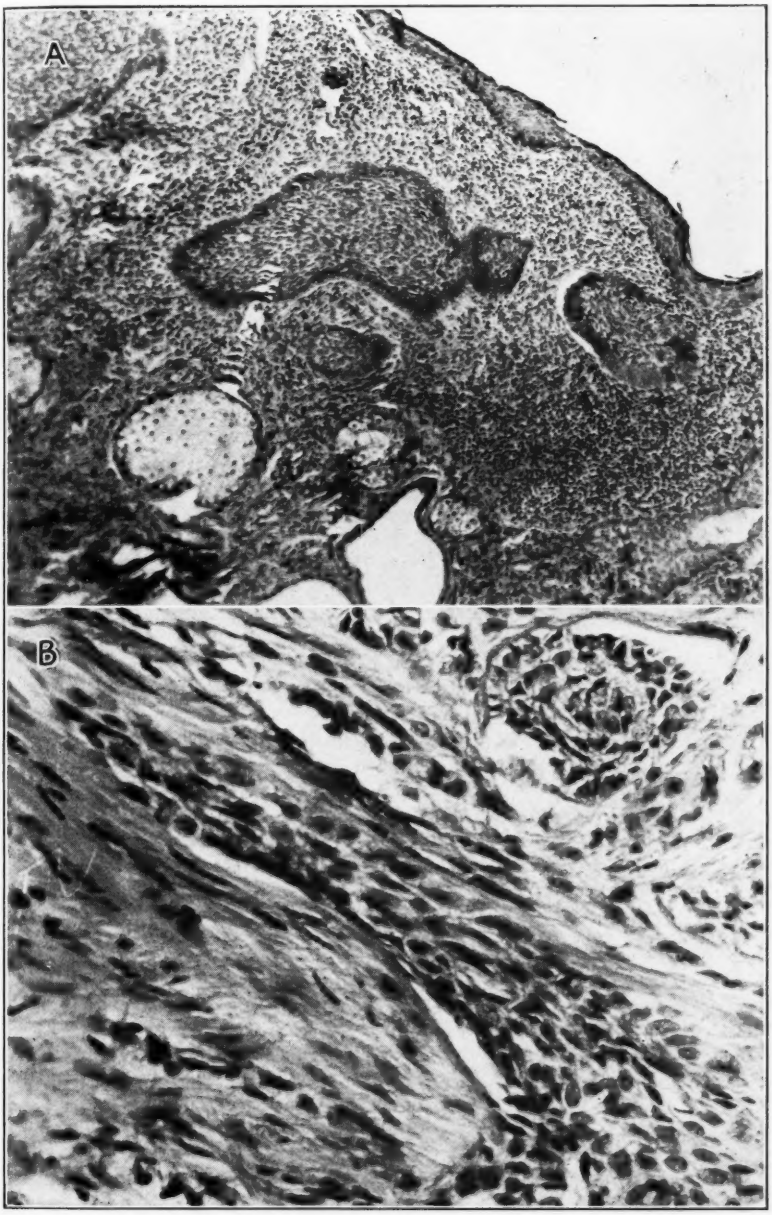

Fig. 5 (case 3).—*A*, section from the excised tumor, showing the basal cell tumor; × 110. *B*, the spindle cell epidermoid tumor; × 440.

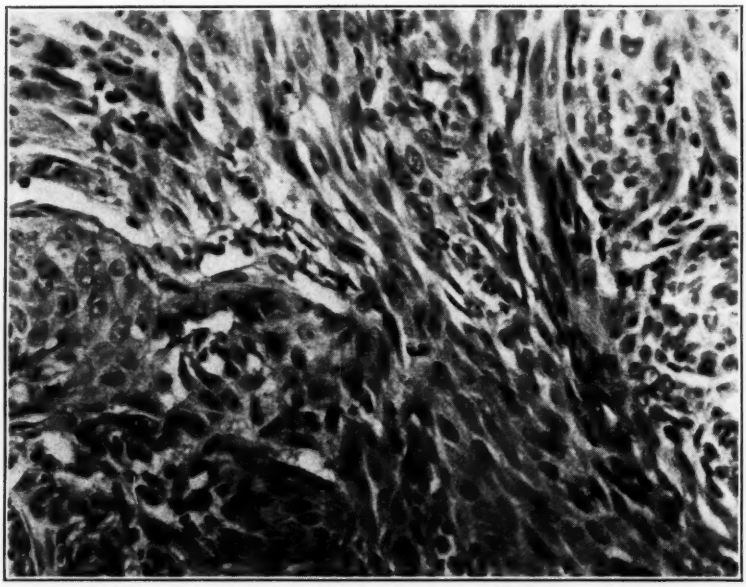

Fig. 6 (case 4).—The whorl-like arrangement can be seen in close apposition to the long strand of spindle-shaped cells in parallel arrangement; × 440.

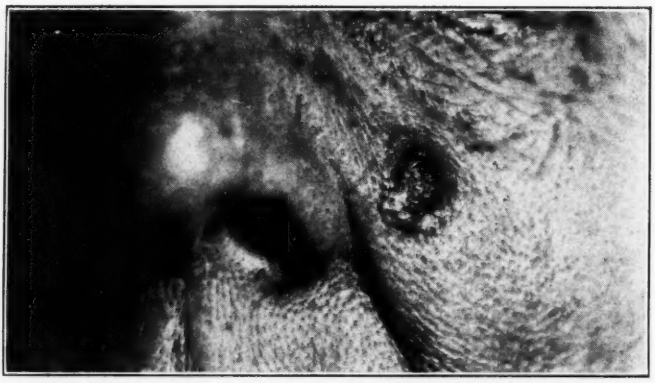

Fig. 7 (case 5).—There is nothing in the clinical appearance to suggest an unusual type of tumor.

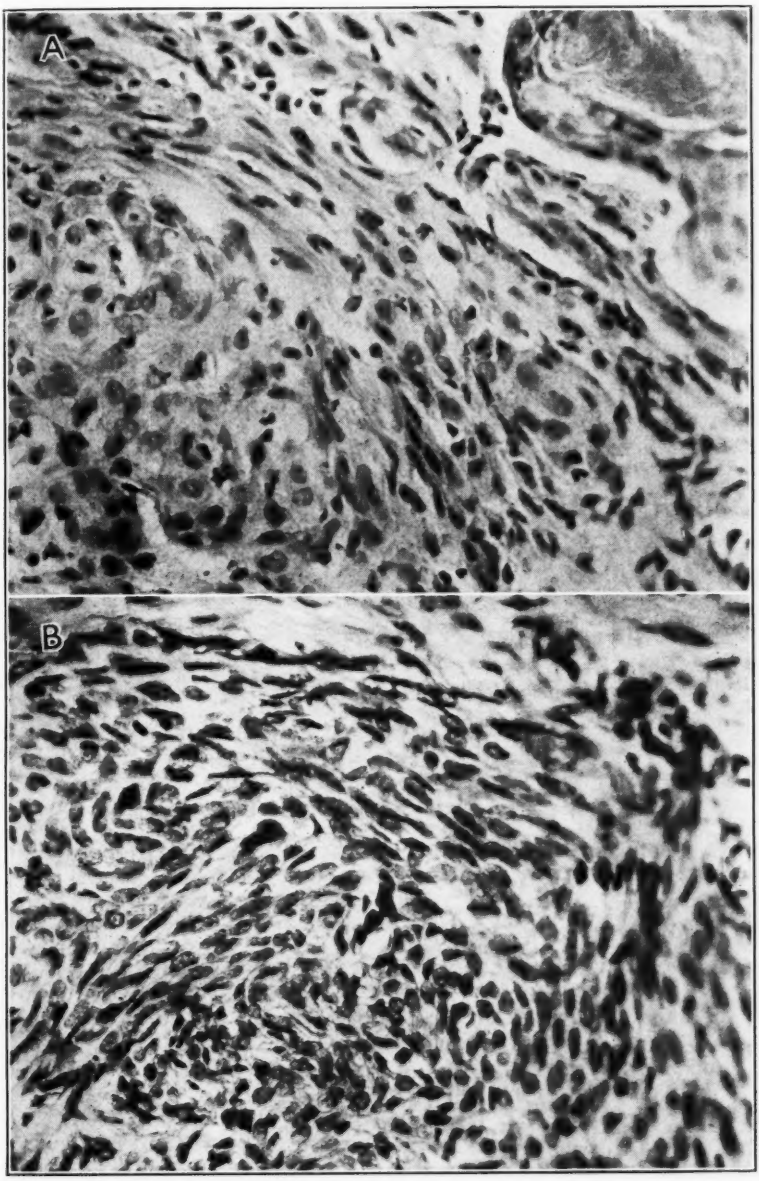

Fig. 8 (case 5).—*A*, section from the biopsy specimen; × 440. *B*, section from the excised tumor; × 440.

stained a faint pink. Some of the nuclei were oval, but most of them were spindle shaped, in spindle-shaped cells. Here and there throughout the mass there were small areas of hemorrhage. Mitotic figures were occasionally seen.

CASE 5.—L. S., a white woman 55 years old, first complained of a mass on her left cheek on July 23, 1945. She had been a patient in New Haven Hospital in 1937 for inactive pulmonary tuberculosis. The mass had been present for one year and was slowly growing larger. On the left cheek near the nose there was an elevated infiltrated nodule with a central crust. The tumor bled freely on removal of this crust. A piece was taken for biopsy and showed the picture of a spindle cell epidermoid carcinoma. The entire mass was excised on Aug. 2, 1945. On August 10 a slight wound infection appeared, and subsequently a pyogenic granuloma developed. After this was destroyed, the wound healed without further incident, and when the patient was last seen, on July 3, 1948, there was no evidence of recurrence. No radiation therapy had been given.

The biopsy section showed a piece of tissue on one edge of which could be seen a stratified, squamous epithelium. This layer dipped down into the underlying stroma and fibrous connective tissue, and a mass of squamous cells were seen which grew through the tissue in sheets and whorls. Some of these whorls had keratotic pearls in the center. Intracellular bridges were seen. The cells were somewhat irregular in size. In some areas spindle-shaped cells could be seen. These were arranged in bundles in a parallel arrangement, with the nuclei assuming a spindle shape.

The excised tumor showed a piece of skin, both ends of which were covered by stratified squamous epithelium. The basal cell layer appeared intact. In the center of the section, however, the epithelial layer had been lost and a mass of cells growing in sheets and nests and strands were seen. Most of the cells had oval vesicular nuclei and a faint pink cytoplasm. Interstitial bridges were seen, and mitotic figures were easily found. Throughout all this mass of cells there were areas where the cells were elongated and spindle shaped, had spindle-shaped nuclei and were arranged in parallel fashion. This observation was particularly noticeable at the lowest part of the tumor where the cells were invading the deeper connective tissue stroma.

COMMENT

Undoubtedly, a large proportion of spindle cell epidermoid carcinomas appear in areas of chronic radiodermatitis and so might be said to be the result of roentgen ray therapy. However, since a not inconsiderable number appear in skin which has never been subjected to and therefore has not been damaged by roentgen rays, it seems likely that there may be other factors which can cause this unusual tumor. The total number of cases reported by Martin and Stewart, Montgomery, Sims and Kirsch and me is 17. The 5 reported here, Martin and Stewart's case 5 and Montgomery's cases, or more than one third of the total number, could not have been caused by roentgen irradiation, as none had been given previous to the first appearance of the spindle cell carcinoma. Martin and Stewart themselves said, in discussing their case 8: "It is possible that spindle-cell carcinoma existed from the beginning." In their case 2, the patient had been subjected to two years of treatment with solid carbon dioxide in addi-

tion to roentgen ray therapy before development of the tumor, and in addition careful reading of the report of their case 1 fails to reveal that the roentgen rays were used on that patient until after removal of the piece of tissue on which the diagnosis of spindle cell carcinoma was made. The lesion had been treated, however, with endothermy and actual cautery. The patient in Montgomery's case 2 was subjected to roentgen rays and the electric needle, but not until after the removal of the initial tumor, which one pathologist had called epithelioma and another, sarcoma. Undoubtedly this lesion was a spindle cell carcinoma from the beginning. Even the patient in case 1 of Sims and Kirsch was treated once by electrocoagulation three months before surgical removal and microscopic examination. So, one might say that only case 2 reported by Sims and Kirsch and Martin and Stewart's

Physical Agents to Which Sites of Tumors Were Subjected Prior to Appearance of Spindle Cell Epidermoid Carcinomas

	Martin and Stewart[2]								Montgomery[3]		Sims and Kirsch[1]		Strauss				
Case number.....	1	2	3	4	5	6	7	8	1	2	1	2	1	2	3	4	5
Roentgen rays....	..	X	..	X	..	X	X	..	..	..	X	X	..	..	..	..	..
Radium	..	X	X	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Trauma	..	..	..	..	X	..	..	..	..	..	..	..	..	..	..	..	..
Burning	X	..	..	..	..	..	..	..	..	..	X	..	..	..	..	..	..
Carbon dioxide...	..	X	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Excessive sunlight	..	X	..	..	..	..	..	..	..	..	..	..	..	X	..	..	..
Nothing	..	..	..	..	..	..	..	X	X	X	..	..	X	..	X	X	X

cases 3, 4, 6 and 7—5 out of 17, less than one third of the reported cases—can be claimed to have completely unclouded titles to the possibility of having been caused by roentgen or radium irradiation. In the 5 cases reported here true scarring was not seen. The tumor in case 2 arose from skin which showed typical senile atrophy, and, in case 4, while there was no noteworthy atrophy, the patient exhibited other lesions commonly seen in senile skins.

Unquestionably these tumors have arisen, in most of the cases, in skin which has been subjected to and changed by some physical agent or in an area which has been either cicatricial or atrophic. Five patients have been exposed to roentgen rays, 1 to radium, 1 to trauma, 1 to ultraviolet radiation, 1 to destructive applications and 1 to roentgen rays and destructive applications. For 2 persons there was no clinical evidence of any change in the surrounding skin or history of a preceding application of any kind.

What causes the development in these epithelial tumors of cells which, although still unquestionably of epithelial origin, nevertheless

take on a form quite different from that of the cells producing them? Apparently it is some change in the tissue in which the tumor arises that gives rise to this mutation.

Martin and Stewart considered the possibility that scar tissue or atrophy may be responsible for the change but admitted that their cases pointed to the fact that the spindle cell morphologic picture may be established independently of the cicatrix.

Perhaps the strongest evidence that the cause is something to be found in the site of the tumor rather than something inherent in the tumor or in the host can be found in the report of a spindle cell epidermoid carcinoma, made by Greene and Brown.[5] This was an epithelial tumor appearing spontaneously in the skin of a rabbit. Three biopsy specimens were taken from this tumor. All three showed squamous cell carcinoma with bands of spindle-shaped cells with regularly placed parallel nuclei. Transplants to the anterior chamber of the eye were made from all three specimens. Transplants from the first two had completely negative results, but transplants from the third were successful in 100 per cent of the animals used. It made no difference whether the material transplanted to the anterior chamber of the eye was predominantly of squamous cells or predominantly of spindle cells. The resulting growth was in every case made up of squamous cells alone. In addition, all the metastatic growths in the original animal, including several metastases to the skin, were made up entirely of squamous cells. Strangely enough, when testicular transplants were attempted, with the use of cellular emulsions of these anterior chamber growths which consisted exclusively of squamous cells, growths resulted which consisted solely of spindle cells and had the same structure and arrangement found in the primary growth. It is noteworthy also that in cases 3 and 4 reported here multiple tumors were excised and in each only one of the growths showed the picture of spindle cell epidermoid carcinoma. In case 2 of Martin and Stewart's series there were multiple epidermoid carcinomas, only the last being of the spindle cell type and in their case 3 were presented two epidermoid carcinomas, one spindle cell and the other the classic type.

One factor that seems to have been present in almost all the cases was pressure, whether due to postradiation atrophy, senile atrophy, scar formation or some other cause. In the cases considered in this article compression might have been caused as follows: in cases 1 and 5 reported by Martin and Stewart, scar tissue; in their case 2, scar tissue and chronic radiodermatitis; in their cases 4, 6 and 7 and both of the cases reported by Sims and Kirsch, chronic radiodermatitis; in case 2 reported here, senile changes in the skin; in case 3, a coex-

5. Greene, H. S. N., and Brown, W. H.: A Transplantable Squamous Cell Carcinoma in the Rabbit, Cancer Research **3**:53-64 (Jan.) 1943.

isting basal cell tumor and proximity to the tarsal plate, and in case 4, compression between elongated hair follicles. In case 5 the spindle cell change is seen most clearly where the tumor is invading the connective tissue. In cases 3 and 8 reported by Martin and Stewart, both of Montgomery's cases and case 1 reported here, there was no apparent compression of the tumor.

Reference to the table shows that in the 17 cases 6 persons had been exposed to roentgen rays, 2 to radium, 1 to trauma, 2 to physical destruction by one means or another, 1 to freezing with solid carbon dioxide and 2 to large amounts of ultraviolet radiation. In 7 cases there was no history of previous insult or damage to the site of the tumor. Two of the patients who had received roentgen ray therapy had also been subjected to other physical agents, 1 to burning with the so-called electric needle; the other to radium, solid carbon dioxide and ultraviolet irradiation.

The data presented suggest that the appearance of spindle cells in an epidermoid carcinoma of the skin does not represent any real change in the tumor. The change appears to be dependent on some factor operative at the site of the tumor and not to something inherent in the tumor itself.

SUMMARY AND CONCLUSION

Five cases of spindle cell epidermoid carcinoma are reported. In none of these had there been any previous exposure to roentgen rays or radium.

The histogenesis of this particular type of carcinoma appears to be dependent on some factor acting at the site of the tumor.

It is suggested that this factor may be compression of the tumor. This element of compression may be caused by several factors, of which chronic radiodermatitis is only one.

41 Trumbull Street.

ABSTRACT OF DISCUSSION

DR. M. D. MARCUS, St. Louis: In the past, spindle cell epidermoid carcinoma has been confused with sarcoma because of the morphologic similarities, and we are indebted to Montgomery, Stewart and Martin and to Sims and Kirsch, for the differentiation of these two neoplasms. In 2 of Stewart and Martin's cases the diagnosis of neurogenic sarcoma was originally made. In 1 of Sims and Kirsch's cases, a diagnosis of sarcoma was entertained. In 1 of Montgomery's cases, the biopsy specimen was identified as squamous cell carcinoma, simulating endothelioma and sarcoma. The other case was thought to be sarcoma by one pathologist. So difficult may the differentiation be that only by tracing the cells back to the epidermis, by the finding of neoplastic squamous (prickle) cells elsewhere in the tissue or by the finding of squamous cell carcinoma in subsequent biopsy specimens can the final diagnosis be made. I feel that the spindle cells should be present in a fairly apparent manner, since scattered spindle-like cells can occur not infrequently in epidermoid carcinomas of the usual variety.

These unusual cancers are nodular, granulomatous or ulcerative and may grow rapidly with lymphatic and blood stream dissemination. The metastasis may be of either spindle or squamous cells. The course of these growths approximates that of squamous cell carcinoma, grade 3 and 4 (Broders' classification). They are radioresistant and do not respond well to endothermy or cautery. Wide excision, when possible, is best. Prognosis may be comparatively poor for life expectancy. Both of Montgomery's patients died with metastases. Of the 8 patients of Stewart and Martin, 4 died of the cancer. Because of the seriousness of this form of cancer, it is most important to separate it from other forms, in which treatment, course and prognosis are extremely different.

Martin and Stewart stated that the incidence was found to be less than 1 per cent of all cancer of the skin at Memorial Hospital from 1930 to 1933. In our material at the Barnard Free Skin and Cancer Hospital, in a period from 1947 to the present, 2 cases were found, which represented an incidence of about 1 per cent of all epidermoid carcinomas. In neither of our cases did previous roentgen or radium irradiation play a role. In one a thermal burn preceded the lesion by ten years.

Dr. Strauss has reported 5 cases of spindle cell epidermoid carcinoma. To me, the sections of cases 1 and 3 were of basal cell epithelioma in which there were areas of spindle basal cells, the type described by Krompecher. In cases 2 and 5, the cells were basal and squamous cells and there were areas of keratin formation. Spindle cells were observed, but in the basal cell portions mostly. I felt that these growths were spinobasal cell epitheliomas. Case 4 suggested an epidermoid carcinoma of the spindle cell type, though again spinobasal cell epithelioma was considered. These sections have been reviewed by the pathologists at the Barnard Free Skin and Cancer Hospital, in St. Louis, and by two other pathologists. They concurred with the opinions I expressed.

The origin of the epidermoid spindle cell is a mystery. Dr. Strauss has postulated that a multiplicity of factors may be present and exert their influence through the medium of compression. However, this suggestion still does not explain the lack of production of the spindle cells in the overwhelming majority of epidermoid carcinomas in which these pressure factors still are present or in other tumors where much greater pressure is built up, such as intracranial neoplasms. The experimental work of Greene and Brown indicates that an important factor is local tissue environment. Some believe that the spindle cell is an anaplastic cell, undifferentiated in the sense that anaplastic cell of grade 3 or 4 (Broders') is. This concept of course does not explain the reason for the peculiar morphologic picture. One must also consider that in the middle and upper portion of the epidermis the prickle cells are elongated and spindle shaped. This morphologic picture can also be seen frequently in the periphery of a large epithelial pearl. Consequently, what we may really have is not so much an undifferentiated epidermic carcinoma as a free cell carcinoma. In their growth as free spindle cells the cells may ever assume greater elongation and bundle arrangement, so as to suggest fibrosarcoma.

Dr. Hamilton Montgomery, Rochester, Minn: Dr. Strauss has made an admirable presentation. Judging from his photomicrographs and lantern slides, I thought all but 1 of his cases presented the histologic picture of squamous cell epithelioma, grades 3 and 4, simulating fibrosarcoma. I reported 2 such cases many years ago.[8] Dr. Laurence J. Underwood has just completed a thesis on squamous cell epitheliomas of the skin which simulate sarcomas, especially fibrosarcomas. He was able to find 40 such cases, and I have since seen 6 cases in the last three months in which the question arose histopathologically among the diagnoses of squamous cell epithelioma, sarcoma, nonmelanotic melanoepithelioma and hemangio-

endothelioma. To this list in differential diagnosis must be added distinction of these tumors from leiomyosarcoma and rhabdomyosarcoma. These tumors are usually of grade 3 or 4 malignancy, and in case of tumors of grade 4 it is sometimes necessary to take multiple sections in order to identify the origin of the tumor cells from the epidermis. Grade 3 and 4 squamous cell epitheliomas simulating fibrosarcoma, as a rule, show very little or no pearl formation.

In about one fourth of the 40 cases that Dr. Underwood and I studied there had been radiotherapy and in still others there was a history of the arising of the tumor in scar tissue. The prognosis in regard to the epitheliomas arising after radiotherapy or recurring after radiotherapy seemed little better than that concerning those in which there had not been previous treatment, but the series is too small to be of significance.

Surprisingly enough, 35 per cent of the 40 patients were alive five or more years after treatment for the squamous cell epithelioma. The 2 patients whose cases I reported in 1935 and who are included in this series are both known to be dead. The clinical diagnosis for 1 was sporotrichosis. In the other, there were multiple lesions which were interpreted as systemic blastomycosis or factitial ulcers. Usually, however, squamous cell epithelioma simulating fibrosarcoma occurs as a solitary nodular lesion most frequently situated on the face.

DR. WALTER LEVER, Boston: It has been my observation that more or less extensive areas of spindle cell formation occur not uncommonly in epidermoid carcinomas of grade 3 or 4. I believe that these spindle cell formations are an expression of the pronounced anaplasia of the tumor cells.

DR. M. J. STRAUSS, New Haven, Conn.: I am sorry not to be able to agree with Dr. Marcus about the nature of the tumors because he and I seem to be in agreement about everything else. However, since Dr. Montgomery appears to agree with me, I shall not go into any further details as to why we call these epidermoid carcinomas. It is true that there is also a typical basal cell epithelioma in case 3. That was shown on the screen. In cases 1 and 5 there are one or two small areas which if looked at alone would possibly lead to a diagnosis of basal cell epithelioma. Indeed, if he saw only those areas, it is more likely that the observer would not believe there was any tumor at all. But those areas are in such pronounced contrast against the background of the main tumor that they only emphasize its epidermoid characteristics.

The patient in case 1 has survived five years, without recurrence. In case 2 the patient died of a cardiac accident two years after excision of the tumor, without recurrence up to that time, and the patient in case 3 had had no recurrence until three and one half years after operation, at which time she was lost track of. There have been no recurrences in cases 4 and 5 after one and one quarter and three and one half years, respectively. These patients are still under observation.

DIHYDROSTREPTOMYCIN IN TOPICAL THERAPY

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THE EXACT role of pyogenic infection in the ultimate outcome of many dermatoses is becoming of increasing interest. As new effective antibiotics become available, the need for studies to determine their effectiveness as against their sensitizing capacities in local therapy is obvious. In continuing our investigations in this field, dihydrostreptomycin seemed worthy of trial.

Herein are reported the clinical results and the bacteriologic observations elicited in the course of treatment of 159 patients with dihydrostreptomycin in various bases. Also presented are the observations relative to the development of drug resistance by some of the organisms encountered. The results elicited in the patch testing of patients never exposed to this antibiotic and of those previously exposed are given.

In 1946 Peck and co-workers [1] and subsequently Bartz and co-workers [2] and Fried and Wintersteiner [3] described independently the preparation of dihydrostreptomycin by the catalytic reduction of streptomycin.

In general this antibiotic has been found to be effective against all gram-positive bacteria, with the possible exception of the clostridia, and against the majority of the gram-negative bacteria. It is reported

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Read at the Sixty-Ninth Annual Meeting of the American Dermatological Association, Inc., at Hot Springs, Va., May 26, 1949.

Supported in part by a grant from E. R. Squibb and Sons. The dihydrostreptomycin preparations were supplied by E. R. Squibb and Sons.

From the Department of Dermatology and the Department of Surgery, Columbia University College of Physicians and Surgeons, the Vanderbilt Clinic and New York City Hospital.

1. Peck, R. L.; Hoffhine, C. E., Jr., and Folkers, K.: Streptomyces Antibiotics: IX. Dihydrostreptomycin, J. Am. Chem. Soc. **68**:1390-1391 (July) 1946.

2. Bartz, Q. R.; Controulis, L.; Crooks, H. M., Jr., and Rebstock, M. C.: Dihydrostreptomycin, J. Am. Chem. Soc. **68**:2163-2166 (Nov.) 1946.

3. Fried, J., and Wintersteiner, O.: Streptomycin: II. Reduction and Oxidation Products of Streptomycin and Streptobiosamine, J. Am. Chem. Soc. **69**:79-86 (Jan.) 1947.

to be less effective than streptomycin against the typhoid and dysentery group. It is equally effective against the tubercle bacillus, according to Donovick and Rake.[4] It is less toxic than streptomycin when given parenterally, notably in the reactions of the vestibular portion of the eighth cranial nerve.

In a previous study of bacitracin, we [5] reported a decided difference in release of the antibiotic from various types of ointment bases, finding a superior release from the oil in water and greaseless carbowax® bases. We have repeated this study with dihydrostreptomycin and find the same superior release from the oil in water and carbowax® bases.

PROCEDURE

All our patients were treated with an ointment containing 5 mg. of dihydrostreptomycin per gram or with compresses containing 5 mg. per cubic centimeter. Bases with the following formulas were used:

Base No.		
1.	Carbowax® 1540	36.00 Gm.
	Carbowax® 4000	18.00 Gm.
	Polyethylene glycol 200	46.00 Gm.
2.	Cetyl alcohol	21.00 Gm.
	Glycerin	21.00 Gm.
	Sodium lauryl sulfate	2.00 Gm.
	Propylparaben	0.02 Gm.
	Distilled water	q. s. 100.00 Gm.
3.	Cetyl alcohol	8.00 Gm.
	White petrolatum	20.00 Gm.
	Light liquid petrolatum	18.00 Gm.
	Propylparaben	0.02 Gm.
	Distilled water	q. s. 100.00 Gm.
4.	White petrolatum	100.00 Gm.

The propylparaben (propyl parahydroxybenzoate) is a preservative which must be added to prevent the growth of molds in the ointments.

The majority of our patients were seen in the outpatient clinic; the remainder were treated in the hospital. Cultures were taken in all cases to determine the organisms present and to test their sensitivity to dihydrostreptomycin and their sensitivity with rough tests to bacitracin and penicillin. Where treatment was continued for more than one week, repeat cultures were made to elicit evidence of development of resistance by the organisms to the antibiotic.

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4. Donovick, R., and Rake, G.: Studies on Some Biological Aspects of Dihydrostreptomycin, J. Bact. **53**:205-211 (Feb.) 1947.

5. Miller, J. L.; Slatkin, M. H., and Johnson, B. A.: Evaluation of Bacitracin in Local Treatment of Pyogenic Infections, Arch. Dermat. & Syph. **60**:106-120 (July) 1949.

The necessity for removal of crusts in pyogenic infections is obvious. For this purpose, we prefer wet compresses, usually of saline solution. Compresses remove crusts painlessly as well as effectively and do not irritate the skin as soap and water may. In a few of our cases we used dihydrostreptomycin compresses entirely. The solutions are prepared by adding sterile water to weighed samples of the antibiotic. These are relatively stable, as 76 per cent of the original amount of antibiotic has still been present after one year in test samples kept at room temperature.

RESULTS

Our standard for adequate follow-up requires that patients be seen several weeks after supposed cure and after stopping all treatment. This fact largely explains the variation between the number of patients treated

TABLE 1.—*Results in Treatment of Primary Superficial Infections of the Skin with Dihydrostreptomycin Ointment*

Diagnosis	Total No. of Cases	No. of Cases Adequately Followed	No. of Cures	No. of Failures	No. of Reactions To Medication	Time Required for Cure, Days		
						Maximum	Minimum	Median
Impetigo contagiosa	32	25	24	1	0	19	2	5
Ecthyma	8	5	5	0	0	12	4	6
Folliculitis of the beard	18	10	4	6	0	17	3	8
Folliculitis elsewhere	16	12	7	5	0	14	4	10
Infectious eczematoid dermatitis	18	12	12	0	1	8	2	5
Otitis externa	9	6	6	0	0	14	2	12
Vesiculopustular eruption of hands	20	13	6	7	2	30	12	20
Acne varioliformis	2	1	1	0	0	..	..	2
Acne vulgaris (pustular)	1	1	0	1	0	..	..	..
Total	124	85	65	20	3			

and those listed as adequately followed. Table 1 shows that of 32 patients treated for impetigo 25 were adequately followed. The median time of cure was five days. One case is listed as showing a failure of treatment; the patient was uncooperative. In 3 of these cases the patients received only dihydrostreptomycin compresses, 5 mg. per cubic centimeter. One patient with impetigo involving both sides of the face was given dihydrostreptomycin compresses on one side and saline compresses on the other. The side treated with the antibiotic cleared in three days; the side given the saline compresses became worse. The procedure was reversed, with clearance of all the lesions in three more days.

In 5 cases of ecthyma the lesions cleared in a median time of six days. In a case of one year's duration there was clearing in seven days.

Clinical and bacteriologic differentiation between simple folliculitis of the beard and the very resistant cases of sycosis vulgaris is almost impossible except on the basis of duration of the infection. In this

series of 10 cases, 4 persons had had their infection one to twenty years, and 5 of the remainder, more than three months. Of the 4 cases listed as having cures, 2 were of long duration. The entire series of patients had been treated with other antibiotics previously, including injections of penicillin in 3 cases. Of the 6 cases listed as showing failure of treatment, 5 have been controlled by administration of the antibiotic, recurring if it is discontinued. The one frank failure occurred in a case of only three weeks' duration and resulted apparently from the development of resistance to dihydrostreptomycin by the organism as shown by repeat cultures. The period of observation is too short in a disease of this character to draw definite conclusions.

In the cases listed as folliculitis elsewhere, 1 patient was treated with ammoniated mercury salve on one extremity and dihydrostreptomycin on the other. Cure occurred on both locations in the same length of time. In another case, penicillin ointment was used on one side and the antibiotic under study on the other; both means of treatment failed.

In 12 cases of infectious eczematoid dermatitis cure resulted in a median time of five days. In this disease patients are prone to have reactions. A questionable reaction was seen in this group. It consisted of a mild vesicular dermatitis in the area under treatment. Treatment was stopped and after several days was resumed, with a recurrence of the vesicular dermatitis. The eruption cleared with the use of a soothing lotion only, and subsequent patch tests in the areas previously involved, both to the antibiotic and to the base, gave negative reactions. One patient who had acquired a dermatitis from injections of penicillin was treated without incident.

In all 6 cases of otitis externa there were cures. Here again the follow-up time is inadequate for any definite conclusions. Three of the patients were treated with 5 mg. per cubic centimeter of dihydrostreptomycin in 50 per cent alcohol, and 3, with an aqueous solution of the same strength. Salves are not indicated in this location as they frequently block the canal.

Under the heading of persons with vesiculopustular eruptions of the hands are listed patients who had had repeated cultures which were negative for fungi and in whom examinations for foci of infection had given negative results. In one half of the patients the condition had been present from one to fifteen years. In the remainder the duration was less than a year. Two reactions occurred in this group. One patient was improving when he acquired a vesicular dermatitis. This patient's eruption cleared with the use of bacitracin ointment. The second patient had a vesicular reaction after using the ointment three weeks. Cultures at this time showed the presence of a dihydrostreptomycin-resistant organism.

In the group of various dermatoses with secondary infection listed in table 2, the antibiotic cured the secondary infection in all except 6 cases. Five of these failures were in cases of ulcers of the legs. After initial improvement, no further changes occurred. Repeated cultures showed the development of resistance to the antibiotic by the organism present in these cases. One reaction occurred among the patients with ulcers of the legs after the ointment had been used for four weeks.

Patch tests were performed on 113 patients who had never had contact with either dihydrostreptomycin or streptomycin. All these tests gave negative reactions. Fifty-seven patients who had been treated with dihydrostreptomycin locally, 4 more who had received streptomycin parenterally and 1 nurse who handled streptomycin were tested. Of the last-mentioned group, 1 patient who had received streptomycin locally

TABLE 2.—*Results in Treatment of Secondary Infection in Various Dermatoses with Dihydrostreptomycin Ointment*

Disease in Which Secondary Infection Appeared	Total No. of Cases	No. of Cases Adequately Followed	No. of Cures	No. of Failures	No. of Reactions To Medication	Time Required for Cure, Days		
						Maximum	Minimum	Median
Contact dermatitis	8	5	5	0	0	14	3	8
Dermatophytosis	9	4	4	0	0	7	6	7
Allergic eczema	7	5	4	1	0	14	5	7
Scabies	4	2	2	0	0	22	14	18
Varicose ulcers	6	6	1	5	1	..	..	..
Acrosclerosis	1	1	1	0	0	..	..	14
Total	35	23	17	6	1			

showed a 4 plus reaction both to dihydrostreptomycin and to streptomycin.

Two patients with open lesions of the skin were given continuous wet dressings of dihydrostreptomycin, and determinations of blood levels were made in twenty-four, forty-eight and ninety-six hours. The highest blood level was 1 microgram, which is a very small amount.

Table 3 summarizes for comparative purposes our experiences with dihydrostreptomycin and those previously reported with bacitracin,[6] penicillin [7] the sulfonamides [8] and nitrofurazone (furacin®) [7] in ointments for the treatment of pyogenic infections of the skin.

6. Miller, Slatkin and Johnson[5]; Local Use of Bacitracin, J. Invest. Dermat. **10**:179-188 (March) 1948.

7. Miller, J. L.; Rodriquez, J. J., and Domonkos, A. N.: Evaluation of Penicillin in Topical Therapy, New York State J. Med. **47**:2316-2321 (Nov.) 1947.

8. Miller, J. L.: Use of Sulfanilamide and Its Derivatives in Ointment Form: Local Treatment of Cutaneous Diseases, Arch. Dermat. & Syph. **46**:379-385 (Sept.) 1942.

TABLE 3.—*Results in Treatment of Superficial Infections of the Skin with Various Chemotherapeutic Agents*

Disease	Ointments Used	Total No. of Cases	No. of Cases Adequately Followed	No. of Cures	No. of Failures	No. of Reactions to Medication	Median Time of Cure, Days
Impetigo contagiosa	Dihydrostreptomycin	32	25	24	1	0	5
	Bacitracin	91	62	60	2	0	8
	Penicillin	115	91	89	2	2	5.8
	Sulfonamide	..	45	44	1	1	6
	Nitrofurazone	18	16	15	1	0	8
Folliculitis of beard	Dihydrostreptomycin	18	10	4	6	0	8
	Bacitracin	54	40	18	22	0	21
	Penicillin	21	15	8	7	2	11
	Sulfonamide	..	12	5	7	1	45
	Nitrofurazone	6	4	3	1	1	12
Folliculitis elsewhere	Dihydrostreptomycin	16	12	7	5	0	10
	Bacitracin	26	17	15	2	0	18
	Penicillin	18	14	13	1	0	10
	Sulfonamide	..	2	1	1	0	42
	Nitrofurazone	5	4	4	0	0	10
Ecthyma	Dihydrostreptomycin	8	5	5	0	0	6
	Bacitracin	39	24	24	0	0	14.5
	Penicillin	21	14	13	1	1	8
	Sulfonamide	..	12	12	0	0	18
	Nitrofurazone	2	2	1	1	0	11
Infectious eczematoid dermatitis	Dihydrostreptomycin	18	12	12	0	1	5
	Bacitracin	38	34	33	1	0	9
	Penicillin	1	1	1	0	0	5
	Sulfonamide	..	..	..	..	..	..
	Nitrofurazone	..	..	..	..	..	..
Secondary infection in allergic eczema	Dihydrostreptomycin	7	5	4	1	0	7
	Bacitracin	26	20	20	0	0	10
	Penicillin	5	4	4	0	0	7
	Sulfonamide	..	5	5	0	0	14
	Nitrofurazone	2	2	2	0	0	11
Contact dermatitis	Dihydrostreptomycin	8	5	5	0	0	8
	Bacitracin	12	7	7	0	0	11
	Penicillin	2	2	1	1	0	..
	Sulfonamide	..	..	..	..	..	..
	Nitrofurazone	5	4	4	0	0	19

TABLE 4.—*Bacteriologic Flora in Primary Infections*

Disease	Total No. of Cases	Coagulase-Positive Staph. Aureus (No Beta Hemolytic Streptococcus)	Beta Hemolytic Streptococcus (No Coagulase-Positive Staph. Aureus)	Coagulase-Positive Staph. Aureus and Beta Hemolytic Streptococcus	Additional Species*
Impetigo contagiosa	31	17	2	12	11
Ecthyma	7	1	0	6	2
Folliculitis of the beard	13	12	1	0	6
Folliculitis elsewhere	20	19	0	1	8
Infectious eczematoid dermatitis	17	5	0	12	6
Otitis externa	8	5	0	3	6
Vesiculopustular eruption of hands	18	11	0	7	5
Acne varioliformis	1	0	0	1	0
Acne vulgaris (pustular)	1	0	0	1	0
Total	116	70	3	43	44
Percentage		60.3	2.6	37.1	37.8

* Coagulase-negative micrococci, nonhemolytic streptococci, diphtheroids, coliform bacilli, a proteus, Ps. aeruginosa, B. subtilis, Cl. perfringens and anaerobic micrococci.

BACTERIOLOGIC STUDIES

The bacteriologic observations are recorded in tables 4 and 5. In the last column are listed various organisms found in certain cultures in addition to the Staphylococcus aureus, the beta hemolytic streptococcus or a combination of the two. These organisms, identified in the footnote, were not specific for any one type of lesion, although the percentage of gram-negative bacilli was high in the ulcers of the leg. It is interesting to note that in 60.3 per cent of the cases the Staph. aureus occurred alone or in combination with the organisms just mentioned. The beta hemolytic streptococcus occurred in only 2.6 per cent of the cases under the same conditions. Staph. aureus and the beta hemolytic streptococcus occurred together in 37.1 per cent of the cases. The percentages for the secondary infections, as shown in table 5, differ

TABLE 5.—*Bacteriologic Flora in Secondary Infections*

Disease in Which Secondary Infection Appeared	Total No. of Cases	Coagulase-Positive Staph. Aureus (No Beta Hemolytic Strepto-coccus)	Beta Hemolytic Strepto-coccus (No Coagulase-Positive Staph. Aureus)	Coagulase-Positive Staph. Aureus and Beta Hemolytic Strepto-coccus	Additional Species*
Contact dermatitis	8	5	1	2	3
Dermatophytosis	9	4	2	3	6
Allergic eczema	8	4	0	4	2
Scabies	3	0	0	3	0
Varicose ulcers	6	3	0	3	5
Arosclerosis	1	1	0	0	0
Total	35	17	3	15	16
Percentage		48.6	8.6	42.8	45.7

* Coagulase-negative micrococci, nonhemolytic streptococci, diphtheroids, coliform bacilli, a proteus, Ps. aeruginosa, B. subtilis, Cl. perfringens and anaerobic micrococci.

from those for the primary infections somewhat, but not to a significant degree.

Cultures were taken of all infections before the institution of dihydrostreptomycin therapy to determine the aerobic and anaerobic organisms present in the lesion and the sensitivity of the bacterial flora to this antibiotic. Material from the infection was inoculated into 0.2 per cent dextrose chopped heart medium and streaked on two 5 per cent blood agar plates, one for aerobic and the other for anaerobic incubation. Replatings on blood agar were made from the chopped heart medium after it had been incubated for forty-eight hours at 37 C. After a blood agar plate had been streaked, three filter paper disks saturated with penicillin solution, 2 units per milliliter, bacitracin solution, 20 units per milliliter, and dihydrostreptomycin solution, 250 units[9] per milliliter, were placed on the plate. Although the concentrations of

9. One unit of dihydrostreptomycin equals 1 microgram.

the three antibiotics used in this test varied widely, they have proved to give a reliable preliminary assay of the relative susceptibility or resistance of bacteria to these antibiotics. Correlation between the results of this disk test and the more accurate broth titration assay shows that organisms which give no zone of inhibition adjacent to the disk have a resistance greater than the average range of sensitivity of the particular species in question. The disk-plate method has additional advantages in that the relative susceptibility to the antibiotic of all organisms present can be judged before such organisms are isolated in pure culture. The acquirement of fastness to streptomycin would be quickly recognized. In certain cases increase in resistance was first evinced by the growth of occasional colonies in the area of inhibition adjacent to the disk. Later cultures would reveal no zone of inhibition, showing that the drug-fast mutants were at that time the predominating organisms in the lesion.

TABLE 6.—*Antibacterial Activity of Dihydrostreptomycin in Vitro*

Organisms	No. Strains Tested	Minimal Inhibitory Concentration Micrograms per Milliliter								
		1	2	4	8	16	32	64	128	>128
Staph. aureus, coagulase-positive	91	23	34	20	8	3	1	..	..	2
Micrococci, coagulase-negative	12	1	5	..	1	..	1	..	..	4
Beta hemolytic streptococci	42	1	9	11	8	7	3	2	1	..
Nonhemolytic streptococci	18	..	3	..	1	3	3	4	1	3
E. coli	10	1	4	5	..	..	..	..	..	..
Aerobacter aerogenes	4	1	2	1	..	..	..	..	..	..
Proteus	2	..	..	..	2	..	..	..	..	..
Ps. aeruginosa	5	..	..	..	1	3	1	..	..	..
Clostridium alcaligenes	1	..	1	..	..	..	..	..	..	..

The disk-plate tests revealed no relation between resistance of individual strains to the three antibiotics so tested. The two strains of hemolytic Staph. aureus definitely resistant to dihydrostreptomycin were sensitive to both penicillin and bacitracin. Strains resistant to penicillin or bacitracin or both were sensitive to dihydrostreptomycin. This was also true of all other species of gram-positive bacteria tested. Development of drug-fastness to dihydrostreptomycin in no instance affected the original sensitivity of the organism to penicillin or bacitracin. All gram-negative species were resistant to both penicillin and bacitracin and varied in their susceptibility to dihydrostreptomycin.

In addition to these disk tests for sensitivity to dihydrostreptomycin, the sensitivity of many of the strains isolated was determined more exactly by assays for complete inhibition of growth in Food and Drug Administration broth[10] containing known concentrations of the anti-

10. Food and Drug Administration broth has the following composition: peptone, 5 Gm.; yeast extract, 1.5 Gm.; beef extract, 1.5 Gm.; sodium chloride, 3.5 Gm.; dipotassium phosphate, 3.68 Gm.; potassium dihydroxyphosphate, 1.30 Gm., and distilled water, sufficient to make 1 liter.

biotic. It was necessary to add 5 per cent human plasma to the broth when the streptococcus was the test organism, although we realized that the resistance of the streptococci would be somewhat increased in this richer medium. The results of these assays are given in table 6.

Because of the etiology of the pyogenic infections studied, the predominant organisms isolated were hemolytic Staph. aureus and a beta hemolytic streptococcus. In addition to the other species listed in table 6, Clostridium perfringens was found in 7 cases. All strains were resistant to dihydrostreptomycin as seen in the disk-plate test, i. e., there was no zone of inhibition adjacent to the disk saturated with 250 micrograms of the antibiotic. Nine of the ten strains of Bacillus subtilis isolated were highly sensitive; one was resistant. The 5 strains of diphtheroids were highly sensitive. The 6 strains of anaerobic gas-producing micrococci were moderately susceptible.

TABLE 7.—*Incidence of Acquired Fastness to Dihydrostreptomycin in Vivo in Forty-Six Cases of Pyogenic Local Infections*

Organisms	No. of Strains Sensitive in Primary Isolation	No. of Strains Persisting in Lesion	No. of Strains Acquiring Drug Fastness	No. of Strains not Acquiring Drug Fastness
Staph. aureus, coagulase-positive	46	37	17	20
Micrococci, coagulase-negative	4	2	1	1
Beta hemolytic streptococci	21	10	7	3
Nonhemolytic streptococci	11	6	1	5
E. coli	6	0	..	..
A. aerogenes	4	1	1	..
Proteus	2	1	1	..
Ps. aeruginosa	5	4	3	1

Repeated cultures during treatment were made in 46 cases. The strains recovered from these infections were studied for the acquirement of drug fastness. All the strains included in table 7 were inhibited by 32 micrograms or less of dihydrostreptomycin, when isolated before treatment was started. A strain was considered drug fast when in the broth assay test the concentration per cubic centimeter necessary for complete inhibition of growth jumped to more than 128 micrograms.

A study of table 7 will show that 80 per cent of the strains of hemolytic Staph. aureus persisted in subsequent cultures of the lesion, while only 48 per cent of the beta hemolytic streptococci persisted. The persistence or disappearance seemed to have no relation to the degree of initial sensitivity. Forty-six per cent of the coagulase-positive strains of hemolytic Staph. aureus that persisted developed drug fastness, while 70 per cent of the beta hemolytic streptococci did. The number of strains of the remaining species is perhaps too small to enable us to draw any definite conclusions regarding the rate of persistence or acquirement of drug fastness, but it is significant that four of the five strains of

Pseudomonas aeruginosa (Bacillus pyocyaneus) persisted during the course of treatment and that three of these four strains developed resistance.

We also analyzed our data for the rapidity with which the strains acquired increased resistance. The results are given in table 8. It will be seen that the great majority of strains which became drug fast acquired this property within the first two weeks of treatment.

COMMENT

Stability of the antibiotic, even in an oil in water ointment base, is no serious problem, as our laboratory tests showed no appreciable loss of the antibiotic after three months.

Release of the antibiotic was found by our laboratory tests to be best from the oil in water and the carbowax® bases. However, because of its relative cheapness and general qualities, we used a petrolatum base in the treatment of 15 cases. It is of interest to note that in this group the

TABLE 8.—*Rapidity of Acquirement of Fastness to Dihydrostreptomycin in Vivo*

Organisms	No. of Strains	Time Before Development of Drug Fastness, Days				
		1-3	3-7	7-14	14-21	21+
Staph. aureus, coagulase-positive	17	2	4	4	3	4
Micrococci, coagulase-negative	1	..	..	..	1	..
Beta hemolytic streptococci	7	..	4	3	..	..
Nonhemolytic streptococci	1	..	..	1	..	..
A. aerogenes	1	..	..	1	..	..
Proteus	1	..	..	1	..	..
Ps. aeruginosa	3	1	2	..	..	..

majority of patients required longer treatment than those in the groups in which the other type of bases were used.

Effectiveness can be studied in table 3, where a favorable comparison of the results with dihydrostreptomycin with those previously reported with bacitracin, penicillin, the sulfonamides and nitrofurazone is found. In the past few years we have studied some 700 cases of pyogenic infections treated with a series of agents, and from these studies we have learned approximately what to expect in these diseases from an effective agent. We feel that dihydrostreptomycin is an effective agent.

Development of drug fastness is one of the major problems in the systemic use of streptomycin. Tables 7 and 8 show that drug fastness did develop following local use of dihydrostreptomycin. As can be seen from table 6, the vast majority of the organisms on primary isolation could be considered sensitive. In spite of a concentration of 5 micrograms per gram, it will be seen in table 7 that approximately 46 per cent of the pathogenic staphylococci and 70 per cent of the hemolytic streptococci that persisted in the cases where repeated cultures were taken developed drug fastness.

In table 8 it will be seen that 75 per cent of the organisms in our series which acquired resistance did so within two weeks. Charts not included here were prepared in an attempt to correlate clinical results with the bacteriologic findings of development of resistance. In 16 of 26 clinical failures there was follow-up with repeated cultures, and 81 per cent showed organisms which had acquired fastness during treatment. These studies indicate an early development of drug fastness by the organisms in a significant percentage of instances. From the evidence, it would seem that the development of drug fastness is of such a degree as to be capable of affecting the clinical results adversely. For these reasons we do not advise prolonged use of this agent.

A vesicular dermatitis developed in 4 patients while they were using the dihydrostreptomycin preparations. Thus the reaction rate was 3.7 per cent. Patch tests performed subsequently in 3 of these cases, even in the previously involved areas, gave negative reactions. The positive patch test reaction to dihydrostreptomycin ointments in a patient who had previously reacted to streptomycin locally suggests that cross sensitization occurs. This reaction rate of 3.7 per cent is of significance, as this agent is intended chiefly for parenteral use.

In conclusion, we believe dihydrostreptomycin in ointment bases 1, 2 and 3 to be an effective agent for the treatment of pyogenic infections of the skin. In cases in which excellent results are not attained rapidly, we feel that prolonged use is not indicated because of the probability of the development of drug fastness. The incidence of reaction of 3.7 per cent is considerably lower than that found with penicillin, the sulfonamides and nitrofurazone but significantly higher than that with bacitracin. Further evidence must be gathered on this point.

CONCLUSIONS

1. Dihydrostreptomycin ointment, 5 micrograms per gram, is an effective agent for the treatment of pyogenic infections of the skin.

2. Formulas of oil in water and greaseless bases yielding a superior release of the antibiotic are given.

3. The antibiotic is stable in bases and solutions.

4. Bacteriologic evidence is presented for the development of drug fastness by a significant number of organisms in a short time during local therapy.

5. Good results with dihydrostreptomycin usually occur rapidly. Prolonged use of the agent is not advocated, as poor results may be due to drug fastness.

6. The dihydrostreptomycin ointment caused a vesicular dermatitis in 3.7 per cent of the patients treated.

371 Park Avenue.

ABSTRACT OF DISCUSSION

DR. JOHN GODWIN DOWNING, Boston: I compliment Dr. Miller and his associates for their excellent research in the evaluation of a new antibiotic for local therapy. In recent years several new antibiotics have been recommended, with an enthusiasm that was soon replaced by disappointment because of the untoward reactions of sensitization.

In the evaluation of a new drug for topical application several factors must be considered. First, what is its advantage over accepted therapy? Is it a more elegant preparation, easier to apply and remove? Has it demonstrated definite bactericidal activity in vitro, and is this activity stable at various temperatures? Does the drug diffuse readily from its ointment bases? Is it more economical than the accepted medication? If expensive, is its cost justified because of the reduction in time of disability and suffering? Is it a sensitizer? Does its use in more or less unimportant local infections sensitize patients and preclude its use in more systemic diseases? All these factors must be considered.

However, one must not develop therapeutic timidity. Investigation must continue for new and more efficient therapy. Well planned and controlled research such as presented to us today is to be encouraged. We have all seen local infections cause serious financial loss and affect the sufferer mentally and physically for months. It is comforting to know that we have several new medications, namely, the furan derivatives, penicillin, tyrothricin, bacitracin, streptomycin and now dihydrostreptomycin. Knowing their deficiencies, one can use them intelligently. The bugaboo of sensitization must not be predominant in our minds. Fortunately many persons have a high refractive index for most drugs. Recently an old patient returned for a new prescription for sulfathiazole ointment which has been his standby for years for his recurrent attacks of sycosis vulgaris. No advice could dissuade him from its use. The antibiotics are designed to clear primary infection. Their use in secondary infection must be carefully supervised. As soon as the infection is relieved their administration should be discontinued and other suitable therapy instituted.

The discovery and use of bacitracin by Johnson and her associates merits great recognition. We recently treated 150 patients having pyogenic infections with bacitracin in an anhydrous grease base and with streptomycin in a water-soluble grease base. The results in primary infections were equally good. Bacitracin produced no sensitization. Because of a local vesicular dermatitis the use of streptomycin had to be discontinued in 1 patient with an infected varicose ulcer and in another with otitis externa. A few persons were treated simultaneously with bacitracin and streptomycin with no evidence of irritation and no decrease in the time required for relief.

The ideal therapeutic approach is by well controlled laboratory studies and observance of the inhibition of the bacterial growth which is produced by a given antibiotic in a suitable ointment base. Laboratory studies were done in some of our cases. However, previous studies have convinced us that clinical improvement does not depend entirely on the reduction of bacterial flora, although within limits reduction does indicate the efficacy of the antibiotic. For local use there is apparently no definite advantage of dihydrostreptomycin over its parent, streptomycin. Comparative tests have shown that both have essentially the same activity in vitro against most bacteria. (Dihydrostreptomycin, editorial, *New England J. Med.* **240**:736-737 [May 5] 1949.) Whether dihydrostreptomycin sensitizes less, time alone will prove. It is only on repeated application that sensitization develops.

In this study on 9 patients previously exposed to either dihydrostreptomycin or streptomycin patch tests were made. One showed a 4 plus positive reaction to both substances. The percentage is too large. Miller stated that he observed reactions

in 3.7 per cent of the group tested. This percentage is about the same as I found in my first group of cases treated with nitrofurazone (Downing, J. G.; Hanson, M. C., and Lamb, M.: Use of 5-Nitro-2-Furaldehyde Semicarbazone in Dermatology, *J. A. M. A.* **133**:299-306 [Feb. 1] 1947). Later studies showed a higher percentage (Downing, J. G., and Brecker, F. W.: Further Studies in the Use of Furacin in Dermatology, *New England J. Med.* **239**:862-865 [Dec. 2] 1948). However, it must be borne in mind that nitrofurazone is intended for local use only, while this agent is intended mainly for parenteral use. I was interested to read in this report that nitrofurazone reacted adversely only once in 36 cases.

I admire the work of this group of physicians and their reports on several different drugs for local therapy. I hope they continue this excellent work. I express my sincere appreciation for the opportunity to read and discuss this paper. It has been of extreme value to me, and I know it will be the same to the medical profession at large.

DR. ARTHUR R. WOODBURNE, Denver: While Chief of the Section on Dermatology of Fitzsimons General Hospital in 1945, I had an opportunity to become acquainted early with streptomycin. In all, at the hospital there were probably 100 or 150 nurses who became contact sensitive to streptomycin by opening ampuls and mixing ampuls. I think five days should be the maximum time of its use since organisms rapidly develop drug fastness and this factor of contact sensitivity is a real problem. We find that bacitracin has less sensitizing reaction and affects the same group of organisms. I feel it will have a much wider use from a topical standpoint.

DR. MARION B. SULZBERGER, New York: I know that we are all grateful to Dr. Miller and his associates for their intensive and careful studies on one antibiotic after another. The present paper, of course, is only one report of a series of studies which they have carried out. My associates and I have had only a little experience with the use of streptomycin ointments, as our group has been concentrating on another antibiotic, aureomycin. With the local use of aureomycin in 2 to 3 per cent concentration in ointments we have had results quite similar to those that Dr. Miller reports for streptomycin. We found aureomycin to have similar drawbacks. While in many cases there is rapid improvement under this therapy, recurrences occur in many of them while treatment is still being given. As for the probable reason for the lack of continued effectiveness, we too believed that it might be due to drug fastness of micro-organisms but did not prove this as Dr. Miller has so beautifully done. While aureomycin has the same drawbacks, it has some great advantages. It is extremely expensive still. One of its chief advantages is its lower sensitizing index. We have as yet seen no cases of dermatitis from it. It was effective in local use in a mouthwash in 2 cases of ulcerative stomatitis of the Sutton type in which everything else had failed. It was also effective in several cases of recurrent herpes simplex and interrupted recurrences when used locally. Dr. Miller has mentioned also the cross sensitization between streptomycin and dihydrostreptomycin. Dr. Distelheim and I had an opportunity to make patch tests on a nurse who sometime before had acquired sensitivity to penicillin, and we showed that the patch test elicited a reaction to streptomycin. When she later began to use streptomycin she promptly acquired a dermatitis from this antibiotic also. We then tested her with both streptomycin and dihydrostreptomycin, and despite the fact that she had had no demonstrable exposure to the latter drug, she showed a strongly positive reaction to dihydrostreptomycin. In this case at least there appeared to be a "cross reaction," exposure to streptomycin having apparently sensitized the patient to dihydrostreptomycin also.

UNDECYLENIC ACID IN TREATMENT OF PSORIASIS

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PLAINFIELD, N. J.

THIS IS a report of the course of 17 persons with psoriasis who were treated with undecylenic acid. Considerable interest in the treatment of psoriasis was stirred up after the article by Perlman [1] in which he reported the beneficial effects of the use of undecylenic acid in patients with psoriasis treated by him. The later report by Perlman and Milberg [2] was similar. With supplies of this drug furnished to me in part by the Wallace Research Laboratories, I proceeded to treat patients with psoriasis under my care. In general, I limited its use to administration in chronic cases which I had observed for long periods, in intelligent, cooperative patients. These patients were told to take 4 to 6 capsules four times a day. Each capsule contained 0.44 Gm. of undecylenic acid. No patient was able to take this amount regularly. Each patient was encouraged to take as large an amount as he could tolerate. An effort was made to administer the drug in this dosage for six weeks.

It was soon found best to start with single capsules given several times a day at hours when they could be best tolerated by the patient. The dose was gradually increased to the maximum amount which could be taken. Occasional patients could take twenty-four capsules a day for a few days, but this dose was unusual. Most patients could comfortably take about 6 to 8 capsules per day each day. Every patient was able to take at least a few capsules.

No severe toxic effects were noted at any time. Abdominal distension, heartburn, belching and diarrhea were frequently noted. Sore throats due to trauma in swallowing so many capsules occurred in several of these patients. No unusual scaling of the normal skin occurred at any time. No patient noticed the development of dandruff. Improvement of itching did not occur; rather itching became more pronounced because of the dryness of the psoriatic plaques on cessation of topical applications. Accordingly it was soon found necessary to allow patients to use plain petrolatum to soften dried plaques which became

1. Perlman, H. J.: Undecylenic Acid Given Orally in Psoriasis and Neurodermatitis, J. A. M. A. **139**:444 (Feb. 12) 1949.

2. Perlman, H. J., and Milberg, I. L.: Peroral Administration of Undecylenic Acid in Psoriasis, J. A. M. A. **140**:865 (July 9) 1949.

uncomfortable and to help allay increased itching which followed cessation of the usual ointment medications. At intervals, various types of plabeco therapy were given in addition to the capsules. This measure helped maintain the patients' efforts to persist on the treatment schedule.

These patients were compared with control patients so that coincidental changes in the skin might be calculated. No definite differences were noted between the two groups. These two groups have been followed since the use of the undecylenic acid was discontinued. The effect of this drug during and after treatment on the changes in the nails was observed. No definite change in the nails occurred.

To summarize these findings, the conclusions drawn are as follows:

1. The average patient can take about 6 to 8 capsules for a sustained period.

2. Severe toxic effects were not observed, but nausea, belching, flatulence, diarrhea and throat irritation occurred in most patients as single or multiple symptoms.

3. No selective improvement of the nails, scalp, palms, soles, penis or other skin areas was noted in comparison with a control group.

4. No definite improvement in this group was noted in comparison with a control group.

5. No scaling of normal skin areas was noted during or after treatment with the drug.

7 Watchung Avenue.

DIFFUSE LEPROMATOUS LEPROSY OF MEXICO (SPOTTED LEPROSY OF LUCIO)

An Obscure Early Description in English

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HONOLULU, HAWAII

LUCIO described in 1852,[1] in Mexico, a remarkable variety of leprosy distinguished chiefly by the appearance of circumscribed erythematous macules on the extremities which went on to vesiculation, superficial necrosis and scarring. Patients presenting these lesions always had more or less extensive anesthesia, and nasal obstruction and loss of eyebrows occurred regularly among them. They did not, however, manifest any of the circumscribed skin lesions associated with the usual forms of leprosy, i. e., hypopigmented macules, nodules (lepromas) or elevated plaques; indeed, Lucio failed to recognize any specific lesions of their skin, aside from the remarkable macules. These macules were so characteristic that they gave rise to the name *lepra manchada,* or spotted leprosy.

It remained for subsequent observers, notably Latapi and Chevez,[2] to establish the fact that in these patients the entire skin is the seat of a uniform and diffuse lepromatous infiltration, which disfigures it very little; it has even been suggested [3] that one might call this form of the disease *lepra bonita,* or pretty leprosy. Clinically, however, diffuse leprosy is anything but pretty; it is the most rapidly progressive form of the disease, often terminating fatally (if untreated) in from five to ten years, as opposed to nearly double this time for ordinary lepromatous leprosy and more than triple it for the tuberculoid (formerly "neural") variety.

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1. Lucio, R., and Alvarado, I.: Opúsculo sobre el mal de San Lázaro ó elefanciasis de los Griegos, Mexico, M. Murguia y Cia, 1852, cited by Latapí.[2]

2. Latapí, F., and Chevez, A.: Lepra lazarina en Mexico, in the Proc. Internat. Cong. Trop. Med. & Malaria **2**:1307, 1948; La lepra "manchada" de Lucio, estudio clínico e histopatológico initial, Mem. Internat. Leprosy Cong. **5**:410, 1948; Rev. Fontilles **2**:197 (Jan.) 1949; Interpretación actual de la lepra de Lucio, Mem. Internat. Leprosy Cong. **5**:1019, 1948; The "Spotted" Leprosy of Lucio: An Introduction to Its Clinical and Histologic Study, Internat. J. Leprosy **16**:421 (Oct.-Dec.) 1948. Romero, A.; Brenes Ibarra, A., and Fallas, M.: Clinical Study of Lepromatous Leprosy in Costa Rica, ibid. **17**:27 (Jan.-June) 1949.

3. Latapí, F.: Personal communication to the author.

Lucio reported this entity under its colloquial name in Mexico in his time, *mal de San Lazaro,* and it has since been called "lazarine leprosy." This has occasioned some confusion, especially since Pardo-Castelló in Havana [4] reported several cases of probable tuberculoid leprosy with bullae and ulceration under this same name and suggested that the term be used to indicate formation of bullae in leprosy.

One of the most remarkable features of this form of leprosy is its extraordinarily limited geographic distribution. It comprises 15 to 20 per cent of the cases of leprosy in Mexico City and about 30 per cent of those in Costa Rica.[2] Only occasional, usually solitary, cases have been seen in other parts of Central America and the West Indies; Obermayer [5] reported 1 case in a Los Angeles–born Mexican boy; and 1 case has been identified in Hawaii.[6]

In many respects, Lucio's variety of leprosy is like ordinary lepromatous leprosy, with gradual onset, generalized involvement of the skin, relatively symmetric nerve involvement, nasal lesions, loss of eyebrows, abundant bacilli, histologically lepromatous infiltrate, frequently positive serologic tests for syphilis, negative Fernández (forty-eight hour) and Mitsuda (three week) reactions to intradermally injected lepromin and progressively downhill course (in untreated cases). In other respects it is unlike ordinary lepromatous leprosy: lesions of the eye are rare; laryngeal lesions are rare; intradermally injected lepromin elicits a severe reaction at the injection site in four to five hours (the Medina reaction [2]); vesicular lesions (the "spots") occur, and, perhaps most extraordinary of all, the classic and almost definitive lesion of lepromatous leprosy, the circumscribed granuloma, the leproma itself, never occurs. It is *lepra lepromatosa sine lepromata.*

Up to the time of Obermayer's report in 1947 [5] it did not appear that there had been any detailed published description of diffuse lepromatous leprosy in the English language. The bullous lesions

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4. Pardo-Castelló, V., and Caballero, G. M.: Lazarine Leprosy: A Peculiar Monosymptomatic Form of Leprosy, Arch. Dermat. & Syph. **23**:1 (Jan.) 1931. Pardo-Castelló, V., and Piñeyro, R.: Lazarine Leprosy: Its Position in the Present Classification of Leprosy, Proc. Internat. Cong. Trop. Med. & Malaria **2**:1317, 1948.

5. Obermayer, M. E.: Diffuse Lepra, Ann. West. Med. & Surg. **1**:225 (Aug.) 1947. Obermayer, M. E.; Bonar, S. C., and Rosenquist, R.: Diffuse Lepra, J. Invest. Dermat. **12**:243 (April) 1949. Becker, S. W., and Obermayer, M. E.: Modern Dermatology & Syphilology, ed. 2, Philadelphia, J. Lippincott & Company, 1947, p. 462.

6. Arnold, H. L., Jr., and Sloan, N. R.: Diffuse Lepromatous Leprosy (Lucio's Spotted Leprosy): Report of a Case Occurring in Hawaii, to be published.

described in leprosy by Lehmann [7] occurred as part of the lepra reaction in a patient with actual lepromatous nodules. Nor was the unusual case reported by Burks and Brunsting in 1941 [8] an example of Lucio's phenomenon, for their patient's recurring bullous lesions left oval, atrophic, depressed, pigmented spots, varying from light brown to purple—not, as with Lucio's lesions, irregular-shaped, depigmented, atrophic scars—and, moreover, they often recurred in the sites of previous bullae.

Such a description has been found, however. On Feb. 5, 1885, His Excellency Walter M. Gibson, Minister of Foreign Affairs and President of the Board of Health of the Kingdom of Hawaii, addressed an inquiry regarding leprosy to the governments of most of the countries of the world in which the disease was to be found. The form of the inquiry was a series of seventeen detailed questions prepared for a similar purpose in 1862 by a committee of the Royal College of Physicians, in England.

The replies to these questions, from private physicians, government physicians, hospitals, boards of health, leprosariums, consuls and even, though briefly, the American Dermatological Association, occupy over two hundred fascinating pages of a pamphlet [9] published in Honolulu in 1886 under the somewhat misleading title of "Leprosy in India." Eight of these pages contain two reports from Mexico, one from the Superior Council of Health and a shorter one from Dr. Joaquin (or Juan?) de Gomez, physician in charge of the "Lazar Department" of the Juarez Hospital. These two reports, though quite independent of one another, are in complete agreement in regard to the "three types" of leprosy (not including, as in the English-speaking world of that day, a "mixed" type); and quotations, in what follows, will be taken from both reports.

> There is in Mexico a malady known as 'Mal de S. Lazaro,' . . . the symptoms of which correspond with the disease commonly known under the name of *Elephantiasis Graecorum,* and which some European doctors have also called leprosy . . . [It] shows itself under the following forms: tuberculosa, anaesthetica, and maculosa . . . Even the common people distinguish them by giving the name of *leoninos* to the tuberculous,[10] *antoninos* to the anaesthetic and *lazarinos* to the macular form, using, at times, the last to designate the three forms. . . . In the opinion of the Council they are varieties of one morbid state, although the symptoms, defining them, differ to such an extent that a superficial observer, or one who has not seen a large number of cases, might

7. Lehmann, C. F.: Leprosy: A Review of Some of Its Unusual Features, Arch. Dermat. & Syph. **37**:175 (Feb.) 1938.

8. Burks, J. W., and Brunsting, L. A.: Lazarine (Pemphigoid) Leprosy, Proc. Staff Meet., Mayo Clin. **16**:488 (July 30) 1941.

9. Leprosy in India (and Leprosy in Other Countries), Honolulu, Daily Bulletin Steam Print, 1886, pp. 178-186.

10. It is difficult but necessary to bear in mind that in 1885 "tuberculous" and "tubercular" meant merely "nodular."

consider them as distinctive forms of one morbid entity, if not as different diseases.[11] . . . The earliest symptoms are different in each of the forms . . . thus in the macular form in the earliest beginning of the disease, when even not defined, there is generally a suppression of sweat, numbness and formication in the hands and feet, which in a little time spreads to the rest of the members, which symptoms precede the anesthesia which becomes more or less complete although the anaesthesia is analgesia, because the sensibility of touch although imperfect is conserved throughout the whole sickness. Afterwards follows the falling out of the eyebrows,[12] the eyelids,[13] and the hair of the arms and body, and extremely rarely that of the head; there presents itself also the drying up of the nasal mucous and obstruction of the nose.[14] Generally the suspension of sweat, the insensibility of the members, the drying up and obstruction of the nasal fossae are the early symptoms of this form which becomes marked in two or three years by the appearance of . . . irregular,[15] gangrenous, even-speckled maculae . . . on the limbs, [which] resolve or ulcerate, leaving then peculiar cicatrices.[16] . . . The duration [in the macular form] is variable but as a rule ranges from six to eight years, rarely more. The tuberculous continues from fourteen to twenty years, and the anesthetic up to thirty years."

It would serve little purpose to quote the reports in regard to the other two forms of the disease; they are described in orthodox terms for the period, as nodular (lepromatous) and anesthetic (maculoanesthetic or tuberculoid) leprosy, respectively.

SUMMARY AND CONCLUSIONS

There is a remarkable variant of lepromatous leprosy known as "diffuse" or "pure diffuse" lepromatous leprosy, or "spotted leprosy of Lucio," which is common in certain portions of Mexico and in Costa Rica but apparently very uncommon elsewhere.

The term "lazarine," from an early Mexican colloquialism applied to this variant of leprosy and to leprosy generally, and more recently to any sort of leprosy with vesicles or bullae, has acquired highly confusing connotations and should be abandoned altogether.

An early and obscure description of this form of leprosy, possibly the first published in English, is reported.

The Clinic, 881 South Hotel Street.

11. Still true today.

12. Loss of eyebrows has long been recognized as virtually pathognomonic of the lepromatous variety of leprosy.

13. "Eyelashes" must have been meant.

14. Another feature peculiar to the lepromatous form of leprosy. According to Latapí it is frequently the complaint which occasions the first visit to a physician.

15. They are frequently irregularly triangular or multilateral.

16. The scars are indeed peculiar: largely on the extremities, they are paper thin, depigmented, sharply outlined and irregular in shape.

Clinical Notes

PARADOXIC EFFECT OF ANTIHISTAMINIC DRUG

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CAMDEN, N. J.

The antihistaminic drugs have been widely and successfully used for treatment of a variety of allergic skin diseases. Urticaria heads the list as far as percentage of cases relieved is concerned. Dermatitis venenata or contact dermatitis is another condition for which these drugs are frequently given to reduce itching.

In common with other medicines, the antihistaminic drugs frequently produce undesirable side effects, such as drowsiness, headache and nausea. It is distinctly unusual, however, for one of them to cause the very disease which it is used to treat. Following are reports of 2 such cases, 1 of urticaria and 1 of contact dermatitis produced by tripelennamine ("pyribenzamine") hydrochloride.

REPORT OF CASES

CASE 1.—Mrs. G. S. C., aged 36, the wife of a physician, had had a chronic recurrent vesicular dermatitis of the fingers and hands for six years. This had been variously diagnosed as pompholyx, a fungous infection and contact dermatitis due to soap, among other diseases. On the supposition that the dermatitis had an allergic basis, the patient was given tripelennamine tablets. She took three, of 50 mg. each, daily for three days with great relief of the itching and inflammation of the fingers and hands. One week later there was a mild exacerbation of the dermatitis and she took another tablet at bedtime. During the night there developed a severe generalized attack of urticaria. The patient had never had urticaria before.

Approximately three weeks later, because of a moderate flare-up of the chronic dermatitis of the fingers, the patient took a tablet of tripelennamine late in the afternoon and another early in the evening. In midevening she had her second attack of urticaria. The tripelennamine was then suspected of causing the hives. Consequently, several days after the second attack had disappeared she was given another tablet. Administration of this was likewise followed by an attack of urticaria. No more of the tripelennamine had been taken since these episodes (February and March 1948), and there had been no recurrence of the urticaria to the time of writing. Scratch and patch tests were not agreed to by the patient.

CASE 2.—H. M., a dentist aged 33, had had pruritus ani for two years. Treatment had been unsatisfactory in spite of such procedures as injection of alcohol. When I first saw the patient, on Aug. 2, 1948, the anus and perianal skin were macerated and excoriated. Surrounding this area and extending to the scrotum, pubes, groins and buttocks there was a follicular dermatitis. Because of the complaint of excessive itching the patient was advised to use cool boric acid compresses and to apply 2 per cent tripelennamine cream. Within one hour after the application of the cream the affected parts became violently inflamed, with edema of the penis and scrotum. No additional cream was applied, and after two weeks of boric acid sitz baths, the dermatitis subsided. A patch test with the 2 per cent tripelennamine cream was then applied to the right arm. The result was positive but was not accompanied by any flare-up of the pruritus ani. A patch

test with a pulverized tripelennamine tablet also had positive results in twenty-four to forty-eight hours, and the erythema persisted for forty-eight hours after removal of the patch.

SUMMARY

Two cases of paradoxic effect of an antihistaminic drug are reported, 1 of urticaria and 1 of contact dermatitis, caused by tripelennamine.

516 Cooper Street.

HAIR AS A PENETRATING FOREIGN BODY IN THE PLANTAR SURFACE OF THE FOOT

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Hairs of various kinds may become impacted in the weight-bearing surfaces of the foot and give rise to localized infection, granulomatous foreign body reaction or both.

A cursory review of texts on surgery and dermatology fails to uncover mention of this condition.

The mechanism of the impaction is thought to be similar to the well known means of driving a needle through a coin, in which the needle is first driven through a cork bottle stopper of equal length. The cork is then placed on the coin and struck a sharp blow with a hard object. The splinting action of the cork prevents the needle from fracturing due to sideward bending. In a similar fashion the mesh of the sock or the pressure in the space between shoe and foot or a combination of both may so hold a hair that, once having gained entrance into a sweat gland duct, it is driven into the tissues by the thrusts produced in walking so that eventually it may completely disappear from view.

Two cases of this type have recently come to my attention.

CASE 1.—There was a complaint of a periodic needle-like pain in the terminal plantar pad of the second digit for a period of a month or more, which occurred on stepping in an unusual way, as in turning. Three or four inspections failed to reveal any abnormality at this site. Palpation finally detected a small area of hardness. The skin was carefully shaved down with a sharp scalpel, and when the papillary layer was reached a pinpoint dark spot was encountered. On being grasped with a fine forceps a hair 5/16 inch (0.80 cm.) in length was extracted. Healing followed. The hair was slightly curved and appeared to be an eyelash or eyebrow hair.

CASE 2.—The second case involved a hair impacted in the tissues under the head of the first metatarsal bone. Pain on standing was present for a period of about one week. On first examination there was slight redness at the site. At the end of a week there appeared to be slight suppuration. When the skin was shaved for detection of a foreign body a minute dark spot was detected. A thin, slightly curly hair ½ inch (1.27 cm.) in length was extracted. It appeared to be of other than human origin. The infection and all symptoms disappeared in several days.

Since both these cases were seen in a three month period, it is suspected that this condition may be relatively common and that the hair is usually overlooked because of inadequate examination and is finally discharged with the pus from the ultimately supervening infection. Detection in the present cases may be explained by the fact that a painstaking observation was made since the first case occurred to me and the second case to my wife.

PROPIONATE-CAPRYLATE MIXTURES IN TREATMENT OF DERMATOPHYTOSIS

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LITTLE ROCK, ARK.

Interest in dermatophytosis was intensified during the second world war by the discovery that this condition ranked second among the cutaneous diseases which accounted for no less than 8 per cent of all hospital admissions in the Army and Navy. The Council on Pharmacy and Chemistry of the American Medical Association appointed a committee (Drs. Weidman, Emmons, Hopkins and Lewis)[1] which submitted a report on "The War and Dermatophytosis" in *The Journal of the American Medical Association* for July 14, 1945. One of the noteworthy comments in this report is the naming of sodium propionate as a useful fungicide.

Fatty acid therapy for mycotic infections was introduced by Peck and his associates.[2] This step followed the demonstration by Peck and Rosenfeld[3] that members of the fatty acid series from C_1 to C_{11} were fungistatic and often fungicidal in proper concentration. As normal constituents of sweat, they are physiologic in origin and thus are less likely to cause local irritation and development of dermatophytids, which are drawbacks in the use of many chemical fungicides.

Peck and associates,[2] reporting on the use of sodium propionate in 51 cases of fungous infections, obtained gratifying clinical results in tinea cruris, tinea versicolor and dermatophytosis of the feet.

In 1943 Keeney[4] demonstrated that sodium propionate adjusted to a p_H of 5.5 was fungistatic for all the common pathogenic fungi. Later he and Broyles[5] treated superficial fungous infections and found sodium propionate to be effective in tinea pedis, tinea cruris, tinea glabrosa, thrush and otomycosis.

In studies in vitro related to the fungistatic effect on Trichophyton mentagrophytes (gypseum) Keeney, Ajello, Broyles and Lankford[6] found propionate-propionic acid ointment to be superior to undecylenate-undecylenic acid, Whitfield's (benzoic and salicylic acid), 10 per cent ammoniated mercury, 5 per cent sulfathiazole and 0.5 per cent tyrothricin ointments. Superiority was also claimed for the antibacterial effect in vitro on Staphylococcus aureus and beta hemolytic streptococci. In fact, the propionate-propionic acid ointment was declared to be as effective as penicillin ointment against the streptococci. Because of its fungistatic and antibacterial action and its slightly superior clinical effect, propionate-propionic

1. Weidman, F. D.; Emmons, C. W.; Hopkins, J. G., and Lewis, G. M.: War and Dermatophytosis, with Special Reference to Treatment and Fungicide Testing, J. A. M. A. **128**:805 (July 14) 1945.

2. Peck, S. M.; Rosenfeld, H.; Leifer, W., and Bierman, W.: Rôle of Sweat as Fungicide, with Special Reference to Use of Constituents of Sweat in Therapy of Fungous Infections, Arch. Dermat. & Syph. **39**:126 (Jan.) 1939.

3. Peck, S. M., and Rosenfeld, H.: J. Invest. Dermat. **1**:237 (Aug.) 1938.

4. Keeney, E. L.: Bull. Johns Hopkins Hosp. **73**:379 (Nov.) 1943.

5. Keeney, E. L., and Broyles, E. N.: Bull. Johns Hopkins Hosp. **73**:479 (Dec.) 1943.

6. Keeney, E. L.; Ajello, L.; Broyles, E. N., and Lankford, E.: Bull. Johns Hopkins Hosp. **75**:417 (Dec.) 1944.

acid ointment was recommended by these authors as the treatment of choice for tinea pedis.

Subsequently, Keeney, Ajello, Lankford and Mary [7] demonstrated in vitro that sodium caprylate ointment completely inhibited the growth of T. mentagrophytes. However, it was inferior to propionate-propionic acid ointment in its vitro antibacterial effect against Staph. aureus and beta hemolytic streptococcus. Clinically, the results obtained with sodium caprylate ointment in the treatment of dermatomycosis of the feet were significantly superior to results previously obtained with other fatty acids.

Sodium caprylate solution has also been reported by Keeney [8] as being effective in the treatment of patients with thrush due to Candida (Monilia) albicans.

In 1946 Hopkins and his co-workers [9] reported their studies in the armed forces on fungistatic agents for the treatment of dermatophytosis. In 44 cases use of sodium caprylate resulted in the highest percentage of improvement during the first two weeks of treatment. Propionic acid preparations approximated undecylenic acids in clinical effectiveness and were superior to them in tinea cruris. In this disease the propionic acid preparations were less irritating.

In an excellent review of fatty acid therapy, Peck and Russ [10] reported their experiences with propionate-caprylate mixtures. Tested by the agar cup plate method, the propionate-caprylate mixture inhibited the growth of T. mentagrophytes to a greater extent than did either fatty acid alone. Clinically, an ointment consisting of 12.3 per cent sodium propionate, 2.7 per cent propionic acid, and 10 per cent sodium caprylate was used in patients with tinea cruris, tinea glabrosa, tinea of the rectum, tinea of the nails, tinea of the hands and feet and Trichophyton purpureum infection of the glabrous skin or of the hands and feet exclusive of the nails. Peck and Russ concluded that the propionate-caprylate combination was more effective than any other fatty acids tried in those diseases. Only two instances of irritation—both in eczematized "ids" of the hands—were encountered in their series of cases.

MATERIALS AND METHODS

Prior to the appearance of the Peck and Russ article, an opportunity was afforded me to evaluate clinically the propionate-caprylate mixtures. In view of the evidence on the fungistatic, fungicidal and antibacterial properties of these fatty acids and their nonirritating and nonsensitizing nature, the combination appeared to be highly promising.

Consequently, patients with tinea pedis were selected for study. The cases ranged from acute primary contact ones to chronic cases which had existed for many years. In the course of selecting patients with tinea pedis, other types of fungous infection were encountered and therefore were included in the study. These included tinea of the hands or arm, tinea capitis, otomycosis and mycotic vulvovaginitis.

Treatment was restricted to those patients from whom fungi could be demonstrated either by smear or by culture. Most organisms were identified by both

7. Keeney, E. L.; Ajello, L.; Lankford, E., and Mary, L.: Bull. Johns Hopkins Hosp. **77**:422 (Dec.) 1945.

8. Keeney, E. L.: Bull. Johns Hopkins Hosp. **78**:333 (June) 1946.

9. Hopkins, J. G.; Fisher, J. K.; Hillegas, A. B.; Ledin, R. B.; Rebell, G. C., and Camp, E.: J. Invest. Dermat. **7**:239 (Oct.) 1946.

10. Peck, S. M., and Russ, W. R.: Propionate-Caprylate Mixtures in Treatment of Dermatomycoses, with Review of Fatty Acid Therapy in General, Arch. Dermat. & Syph. **56**:601 (Nov.) 1947.

methods, although in a few cases cultures were negative. Fresh smears were prepared by maceration of the scrapings in sodium hydroxide. For routine culturing, Sabouraud's agar or broth was used. Dextrose agar and occasionally carrots served as culture mediums. The results of laboratory identification are summarized in the accompanying table.

The following procedure was adopted for the treatment of patients with tinea pedis or tinea of the hands and arms. The infected part was washed thoroughly with soap and water and allowed to dry. The propionate-caprylate ointment (ointment "sopronol" propionate-caprylates compound, containing sodium propionate, 12.3 per cent; propionic acid, 2.7 per cent; sodium caprylate, 10 per cent; zinc caprylate, 5 per cent; and dioctyl sodium sulfosuccinate, 0.1 per cent) was rubbed into the area in the evening. The next morning the remaining ointment was removed with alcohol or soap and water and, after drying, the propionate-caprylate powder (powder "sopronol" propionates-caprylate compound, consisting of calcium propionate, 15 per cent; zinc propionate, 5 per cent; zinc caprylate, 5 per cent, and propionic acid, 0.25 per cent in a talc base) was dusted on the lesions. Powder was also dusted into the patient's socks.

Results of Laboratory Identification

Initials	Age	Site	Infecting Organism	Smear	Culture
A. N.	35	Feet	Trichophyton gypseum	+	+
P. R.	25	Foot	Trichophyton schoenleini	+	+
A. A.	19	Foot	T. gypseum	+	+
B. G.	24	Foot	Trichophyton	+	—
B. G.	24	Toe	T. gypseum	+	+
E. M.	74	Foot	Unidentified	+	—
M. P.	..	Foot	Staphylococci	+	—
G. F.	21	Feet, hands	Unidentified	+	—
F. P.	30	Toe, hand	Trichophyton	+	—
W. R.	15	Toe	Trichophyton megnini (gallinae)	+	+
M. H.	29	Toes	Trichophyton schoenleini	+	+
F. C.	20	Toes	C. albicans	+	+
A. W.	8	Arm	Epidermophyton floccosum	+	+
S. L.	59	Hand	E. floccosum	..	+
A. J.	..	Hands, arm	Trichophyton	+	—
E. L.	24	Ear	E. floccosum	+	+
M. W.	51	Ear, neck	E. floccosum	+	+
R. K.	48	Ear, neck	E. floccosum	+	+
G. A.	8	Scalp	Microsporum	+	..
T. W.	..	Scalp	Microsporum	+	..
D. W.	8	Scalp	Microsporum	+	..
M. B.	..	Scalp	Microsporum	+	..
J. N.	25	Vagina	C. albicans Geotrichum	+	..
M. N.	26	Vagina	C. albicans	+	+
L. M.	..	Vagina	C. albicans	+	..

In the treatment of otomycosis, the lesions in the ear and on the neck were swabbed daily with propionate-caprylate ointment and dusted with the powder.

Two of the 3 patients had an extension of the infection onto the lobe of the ear and the surrounding skin of the face and neck. The propionate-caprylate ointment was rubbed into the scalp of the 4 patients with tinea capitis; powder was also used for 1 of these patients. Three patients with vulvovaginitis were treated with "propion gel" (a water-miscible jelly containing calcium propionate, 9.5 per cent; sodium propionate, 9.5 per cent, and propionic acid, 1.0 per cent, in a base containing propylene glycol, 10 per cent, and bentonite, 32 per cent) in the manner prescribed by Carter and associates,[11] i. e., instillation by vaginal applicator for a three week period.

CLINICAL RESULTS

Fifteen cases of tinea pedis or tinea of the hands and arms were treated. Most of the lesions were intertriginous, involving the toe webs and often the nails; a few were dry papulosquamous lesions. The sole of the foot was involved more frequently than the dorsum. The infecting organisms were usually species of Trichophyton or Epidermophyton.

The criterion for clinical cure was the disappearance of itching, scales and vesicles. In cases with early minimal involvement improvement was shown within three to five days and clinical cure within two to three weeks. In advanced cases with considerable denudation of the skin there was likely to be secondary infection with streptococci or staphylococci; specific treatment directed against these bacterial invaders aided the clinical cure, which was observed in four to five weeks.

A recurrence of undetermined origin occasionally occurred in a case of tinea pedis. Prophylactic treatment, particularly with propionate-caprylate powder, following clinical cure avoids recurrence.

All 3 patients with otomycosis were clinically cured within a three week period in spite of the extensive involvement of the skin surrounding the ear in 2 cases.

The 4 patients with chronic tinea capitis showed clinical improvement, but treatment did not result in a cure. This result substantiates the observation by Peck[12] that manual epilation under the Wood light at least once a week is of prime importance in obtaining a cure in a large percentage of the patients treated with local medications. Carrick[13] reported that fatty acid ointments may be employed to good advantage when roentgen ray epilation is not available or practical.

Three patients with vulvovaginitis caused by C. albicans were treated with "propion gel." The infection responded readily to treatment in 2 of the patients. In a third an apparent clinical cure was obtained but a subsequent attack occurred. It was not determined whether this was a relapse or due to a reinfection.

SUMMARY AND CONCLUSIONS

Propionate-caprylate mixtures in ointment and powder forms are clinically effective in the treatment of tinea infections due to species of Trichophyton or Epidermophyton. They proved superior to other local medications used in 10 patients observed during this study.

Secondary bacterial invasion prolongs infections incited by fungi. In such cases, the healing of lesions is expedited by specific antibacterial therapy to supplement the fungicidal action of propionate-caprylate mixtures.

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11. Alter, R. L.; Jones, C. P., and Carter, B.: Am. J. Obst. & Gynec. **53**:241 (Feb.) 1947.

12. Peck, S. M.: Pennsylvania M. J. **50**:569 (March) 1947.

13. Carrick, L.: Methods of Local Therapy for Tinea Capitis Due to Microsporon Audouini, J. A. M. A. **131**:1189 (Aug. 10) 1946.

No instances of irritation or sensitivity were observed. This result reflects the physiologic nature of these fatty acids and is in contrast to effects caused by the irritating and sensitizing properties of many chemical fungistatic agents.

Supplies of the powder, ointment and gel used were provided by Wyeth Incorporated, Philadelphia.

This work was done while the author was chief of the Laboratory, the Alexander Blain Hospital, Detroit. Dr. L. B. Heavner of that hospital gave clinical assistance.

University of Arkansas School of Medicine.

CLINICAL EVALUATION OF PHENINDAMINE (THEPHORIN®) OINTMENT FOR RELIEF OF ITCHING

Preliminary Report

JOHN F. MADDEN, M.D.
ST. PAUL

Phenindamine (thephorin®) is an antihistaminic drug manufactured by Hoffmann-La Roche, Inc. It is a polycylic amine, the empiric formula of which is $C_{19}H_{19}N$ (2-methyl-9-phenyl-2, 3, 4, 9 tetrahydro-1-pyridindene). This study is entirely a clinical one; therefore the chemical, pharmacologic and physiologic aspects of phenindamine will not be discussed. The ointment employed contained 5 per cent phenindamine hydrogen tartrate in carbowax® 1500. It is a white, odorless salve which is easily applied, does not stain and can be washed off with plain water. The treatment was used on patients of all ages and both sexes. The patients were engaged in the usual variety of occupations and showed the variations in personal hygiene commonly seen in private practice.

The cases used in this study were selected. Only those eruptions for which it was thought proper to use an ointment were chosen. The lesions were generally dry. Vesicular, pustular, secondarily infected or weeping eruptions and those accompanied by cellulitis, lymphangitis, acute lymphadenitis or fever were excluded. The accompanying table shows the results of this study.

Of the total 141 patients, 127, or 90 per cent, had relief from itching or complete cessation of the itching. Some of the most startling and dramatic results occurred in cases of pruritus ani and vulvae. Several patients who had had these eruptions for years, some for as long as twenty years or more, were relieved a few minutes after the first application and continued to get relief for the three months that they were observed. The patients with atopic eczema, lichen chronicus simplex, insect bites, nuchal eczema and senile pruritus also were decidedly benefited.

The 7 persons, 5 per cent, who experienced no change in the pruritus were 2 patients with contact dermatitis, 1 with poison ivy dermatitis, 3 with neurotic

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Material for this study was furnished by Hoffmann-La Roche, Inc., of Nutley, N. J.

From the Department of Dermatology, Ancker Hospital, St. Paul, John F. Madden, M. D., Director, and the Division of Dermatology and Syphilology, University of Minnesota Medical School, Minneapolis, Dr. H. E. Michelson, director.

excoriations and 1 pregnant woman with generalized pruritus. It is interesting to note that phenindamine ointment had no effect on neurotic excoriations. This may be explained by the fact that the urge to scratch is so intense and short lived that the patient will not take time to apply local medications. Once the lesions have been produced the sites no longer itch.

In the 7 cases, 5 per cent, in which there was an increase in itching and aggravation of the dermatitis while phenindamine ointment was used the disorder might not have been aggravated by phenindamine ointment at all. It might have become worse if anything else or nothing had been used. The lesions of atopic eczema in an 8 month old baby became acute and weeping. In the 4 cases

Results of Use of Phenindamine Ointment for the Relief of Itching

No. of Cases	Diagnosis	Effect on Itching: Relieved or Stopped Entirely	Effect on Itching: No Change	Effect on Itching: Itching and Dermatitis Aggravated
10	Atopic eczema	9	..	1
15	Pruritus ani	15	..	..
27	Lichen chronicus simplex (localized neurodermatitis)	23	..	4
5	Dyshidrosis	3	..	2
17	Contact dermatitis	15	2	..
5	Poison ivy dermatitis	4	1	..
5	Insect bites	5	..	..
2	Seborrhea of the face	2	..	..
3	Sunburn	3	..	..
8	Pruritus vulvae	8	..	..
5	Urticaria	5	..	..
6	Nuchal eczema	6	..	..
4	Senile pruritus	4	..	..
4	Lichen planus	4	..	..
5	Psoriasis	5	..	..
3	Neurotic excoriations	..	3	..
8	Generalized pruritus without eruption	7	1	..
2	Intertrigo	2	..	..
1	Morphea	1	..	..
2	Dermatitis herpetiformis	2	..	..
4	Dermatitis of the external auditory canals	4	..	..
141	Total	127	7	7
	Per cent	90	5	5

of lichen simplex chronicus the lesions became red, a burning sensation developed and the itching became more intense. The patients had lesions on the upper eyelids where the ointment could not be tolerated in any instance. In the 2 cases of dyshidrosis vesicles developed and pruritus increased. The ointment often produced a momentary burning sensation when it was first applied.

It must be clearly understood that I do not claim that phenindamine ointment cures the aforementioned dermatoses. In self-limited disorders, phenindamine ointment generally relieved the itching and allowed the eruptions to heal without the complications caused by scratching and secondary infection. If the eruptions were not self limited, phenindamine ointment relieved the itching only while it was being used.

In many cases additional therapy such as the administration of phenobarbital, antihistaminic drugs by mouth and low voltage superficial roentgen rays, colloidal baths and wet packs was given. In spite of this the itching was not relieved until phenindamine ointment was used.

Several patients used the ointment from June until the time of this report, in September. If it was effective, the ointment generally did not lose its value over that period. When the ointment was beneficial, relief was usually experienced a few minutes after the first application. A trial of at least one week was given in all cases unless the eruption became aggravated or underwent involution.

SUMMARY

1. One hundred and forty-one patients with various selected dermatoses were treated with phenindamine ointment for the relief of itching. Ninety per cent experienced relief or complete stopping of the itching, 5 per cent showed no effect, and 5 per cent had aggravation of the itching and dermatitis when the ointment was used.

2. Phenindamine ointment is by far the best single agent that I have ever used for relief of itching in the type of cases favorably reported here.

3. This study helps confirm Shelmire's [1] enthusiastic report.

1. Shelmire, I. B.: Experimental Topical Treatment with Thephorin, Postgrad. Med. **4**:443-446 (Nov.) 1948.

SPIEGLER-FENDT SARCOID

Report of a Case

ADOLPH ROSTENBERG, M.D.
AND
WILLIAM M. SISKIND, M.D.
BRONX, N. Y.

Spiegler-Fendt sarcoid is a rare dermatosis. Its exact nosologic position is not determined. Lewis [1] in 1935 divided this disease into the localized and disseminated types. The localized form is superficial and easily destroyed by roentgen ray, arsenic or excision. The disseminated form is deeper, is related to lymphoblastoma or lymphocytoma and is therefore malignant. Montgomery [2] stated that the localized form is a primary cutaneous lymphosarcoma of low grade malignancy and that it may become disseminated and thus end fatally.

Caro [3] in 1941 presented a patient whom he had shown twice before, i. e., in 1930 and in 1935, in whom new lesions had appeared over a period of five or ten years. Repeated studies of the blood revealed no abnormalities. Cippolaro [4]

1. Lewis, G. M.: Is Spiegler-Fendt Sarcoid a Clinical or Histologic Entity? Arch. Dermat. & Syph. **31**:67 (Jan.) 1935.

2. Montgomery, H., in Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943, p. 816.

3. Caro, M. R.: Spiegler-Fendt Sarcoid (Localized Form), Arch. Dermat. & Syph. **43**:1066 (June) 1941.

4. Cippolaro, A. C.: Spiegler-Fendt Sarcoid, Arch. Dermat. & Syph. **53**:166 (Feb.) 1946.

presented a patient with a somewhat similar case in 1946, in whom new lesions appeared after treatment of the first lesion in 1936. From these reports and others in the literature, it can be seen that cases of Spiegler-Fendt sarcoid must be watched for many years. Therefore the prognosis as to the ultimate outcome must be guarded. Clinically, the lesions may simulate sarcoid of Boeck or Darier-Roussy sarcoid; the condition may look like dermatitis medicamentosa or even lymphangioma circumscriptum, so that the exact diagnosis should be made only by pathologic examination.

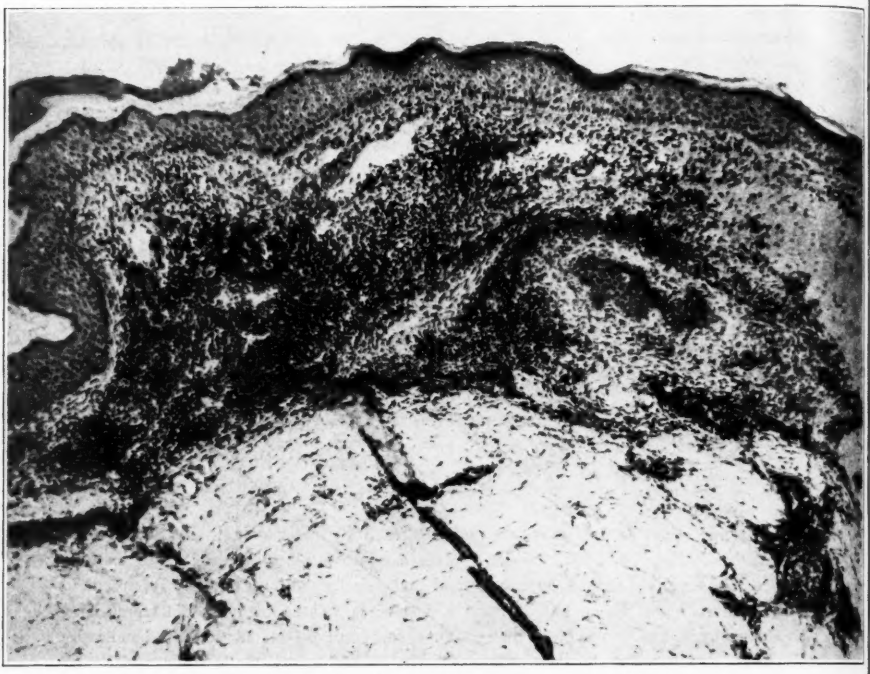


Fig. 1.—Spiegler-Fendt sarcoid, low power magnification.

REPORT OF A CASE

D. S., a married woman aged 25, mother of a 3 year old child, consulted us on May 6, 1948, for a lesion on her right breast. She stated that about eight months ago a small reddish spot had appeared on the right breast and that it had gradually become larger. There was no pain or pruritus associated with it. The family history was noncontributory; the past personal history was irrelevant; results of a complete physical examination were normal; the hemogram was normal, and the serologic test for syphilis gave negative reactions.

Examination revealed an irregularly shaped lesion on the upper region of the right breast, measuring about 4 cm. by 2 cm., red and slightly raised above the surface. Throughout the lesion several yellowish papules were visible. On palpation the lesion felt soft and velvety. Our tentative diagnosis was Boeck's sarcoid or lymphangioma circumscriptum. The lesion was widely excised.

Pathologic Report (by Dr. Wilbert Sachs).—Throughout the cutis there were several large cellular masses. One was present in the subepidermic region, and the other was in the deep cutis. The epidermis was slightly acanthotic. The palisade layer was intact and contained some pigment. The granular and horny layers were present. There were no noteworthy changes in the epidermis. The cellular masses were composed chiefly of small round cells and epithelioid cells.

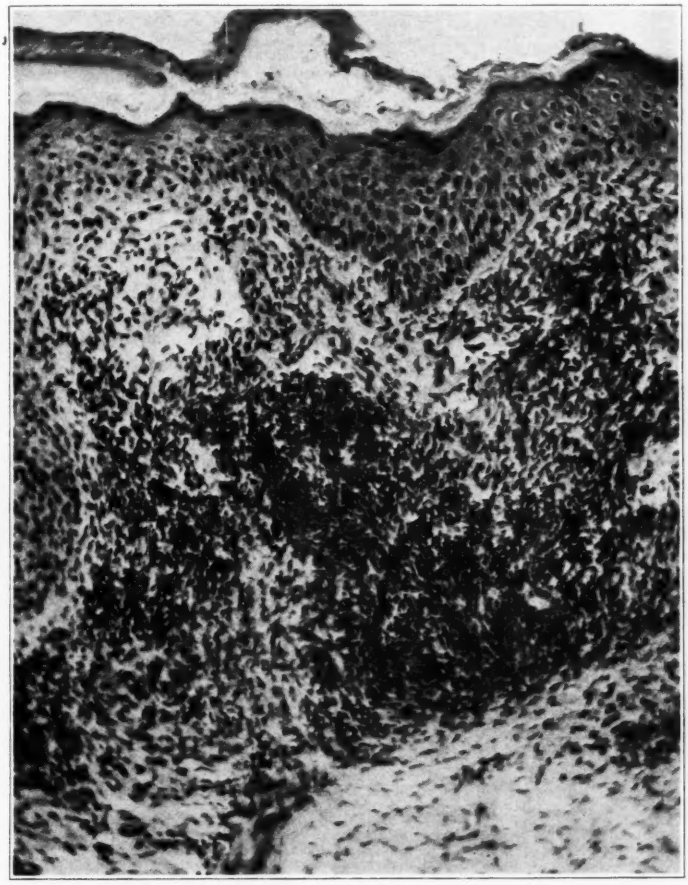


Fig. 2.—Spiegler-Fendt sarcoid, high power magnification.

About the outlying vessels was a pronounced focal infiltration of small round and wandering connective tissue cells. Most of the small round cells suggested the appearance of true lymphocytes. There was a slight interstitial edema of the cutis.

Diagnosis.—The diagnosis was Spiegler-Fendt sarcoid.

There had been no recurrence to the time of writing.

152 East One Hundred and Seventy-Ninth Street (53).

SYNTHETIC COAL TAR SOLUTION

THOMAS BUTTERWORTH, M.D.

With the Technical Assistance of Thomas A. Manzelli, B.S., and Vance E. Brumbaugh, B.S.

READING, PA.

The solution of coal tar is prepared as follows:

	Gm. or Cc.
Coal Tar	200
Quillaia, in moderately coarse powder	100
Alcohol, a sufficient quantity to make	1,000

After mixing the coal tar with 700 cc. of alcohol, add the quillaia and macerate the mixture during seven days in a closed vessel, with occasional agitation. Then filter, and wash the contents of the filter with a quantity of alcohol sufficient to make the product measure 1,000 Gm. or cc.

The procedure described is an unpleasant, time-consuming and labor-consuming process which yields variable results. The color of the product differs according to the origin of the tar as well as in the same tar. In spite of care, small particles of pitch frequently pass through the filter and are objectionable to the patient, especially when the compound is used on light-colored hair. For example, blondes often object to the brown color of scalp lotions containing coal tar solution. Because ethyl alcohol is used in the extraction, the cost of the finished product is high. As a result of these drawbacks, a search has been made for a suitable substitute.

In order to eliminate the preceding objections, my associates and I have attempted to synthesize a solution of coal tar. In 1939, Guy, Jacob and Weber [1] reported on the use of a synthetic tar paste. Later, Saunders and Davis [2] confirmed the efficacy of a kindred preparation. In our work, we have used in the proportions given the active ingredients recommended by Guy, Jacob and Weber. Because of the great difference in cost, isopropyl alcohol has been successfully substituted for ethyl alcohol. The following formula has been used in making 1,000 cc. of synthetic coal tar solution:

	Gm. or Cc.
Anthracene	2.2
Naphthalene	21.8
Phenanthrene	8.0
Carbazole	4.6
Picolene	1.16
Pyridine	1.16
Quinolene	1.16
Phenol	1.4
Cresol	1.5
Isopropyl alcohol 99%, a sufficient quantity to make	1,000.0

The phenanthrene is dissolved first in the alcohol, after which procedure the other ingredients may be added in any order. The result is a straw-colored solution which darkens with age.

From the Department of Dermatology, the Reading Hospital.

1. Guy, W. H.; Jacob, F. M., and Weber, F.: Synthetic Tar Paste: A Therapeutic Suggestion, Arch. Dermat. & Syph. **40**:90-91 (July) 1939.

2. Saunders, T. S., and Davis, W. C.: Clinical Experience with an Ointment of Synthetic Coal Tar, Arch. Dermat. & Syph. **55**:683-685 (May) 1947.

We have used the synthetic coal tar solution where formerly solution of coal tar N. F. was employed. Most frequently, it has been prescribed in a scalp lotion for seborrhea. The following formula, which produces a practically water-colored preparation, has been used with satisfaction:

	Gm. or Cc.
Synthetic coal tar solution	15.0
Salicylic acid	4.0
Spirit of camphor	20.0
Isopropyl alcohol 70%, a sufficient quantity to make	240.0

Synthetic coal tar solution has been used in lotions, in baths (60.0 to 90.0 cc. to a tub) and in full strength when it is applied to the scalp in psoriasis. It has also proved effective in treating palmar eczema when the preparation containing synthetic coal tar solution, 40.0 cc., and glycerine, 20.0 cc., is massaged in gently three or four times a day. We feel that the therapeutic efficiency of the synthetic coal tar solution approximates that of solution of coal tar N. F. From an esthetic viewpoint, it is definitely superior since it is less likely to discolor the hair.

SUMMARY

The preparation of a synthetic coal tar solution and its comparison with a well accepted formula are described. The synthetic preparation is a straw-colored liquid free of pitch, constant in composition and low in cost. Its therapeutic power equals that of solution of coal tar N. F.

CONTACT DERMATITIS DUE TO TABLE CLOTH COVER OF VINYL PLASTIC FABRIC

OTTO B. HITSCHMANN, M.D.
NEWARK, N. J.

This is a report on allergic contact dermatitis from plastic table cloth covers observed on 2 patients. No description of any similar case was found in the literature.

REPORT OF CASES

Case 1.—Mrs. R. R., aged 20, was seen by me on Jan. 4, 1947, for the first time. She showed an erythematovesicular, partly bullous, oozing and crusted dermatitis symmetrically distributed on the ulnar and ulnovolar surface of both forearms. There was a sharp borderline between the eruption and the normal surrounding skin. The diagnosis of allergic eczematous contact type dermatitis was made.

Several substances (chlorox,® abrasive soap powders used in the household and a black lining in a coat, among others) to which the patient had been exposed could be excluded as causative agents, as a contact with those substances would have been unlikely to produce the sharp demarcation and localization on the forearms. After further questioning the patient remembered that recently she had bought a transparent table cloth cover. When she was sitting at the table her forearms rested on or touched the plastic table cloth cover at the very area where the dermatitis was located.

From the New York Skin and Cancer Hospital, Department of Dermatology and Syphilology, New York University Post-Graduate Medical School, Dr. Marion B. Sulzberger, Director.

The patient was asked to avoid further exposure to the table cloth cover. A patch test applied on January 9 with the plastic table cover material showed a 3 plus reaction (fig. 1). At that time the dermatitis had faded. Nevertheless, there were still visible scales and crusts of the applied lotion marking the exact localization of the dermatitis (fig. 2). At the same time the patient was given patch tests with other plastic fabrics used in her house, such as a toaster cover, a yellow plastic tablecloth, a shower and window curtain and a shower cap, all of which did not cause a positive reaction.

Fig. 1.—Reaction (3 plus) to patch test with vinyl plastic tablecloth cover material.

Fig. 2.—Scales and crusts marking the exact localization of contact with plastic vinyl tablecloth cover.

When the patient was seen last, on January 23, the dermatitis had completely subsided. The patient could not be induced to return for further tests.

Case 2.—Mrs. R. W., aged 42, was seen on Sept. 5, 1947. She showed lesions similar to those of the first patient, in identical locations. The patch test with a printed vinyl plastic tablecloth gave a 3 plus reaction. Patch tests with a standard tray of common eczematogenic allergens had negative reactions except for 2 plus reactions to sodium arsenate and to turpentine; both reactions appeared to be responses to primary irritants rather than the specific eczematous type of reaction. The reaction to formaldehyde solution was negative. The arms healed when the table cover was removed and further contact with it avoided.

COMMENT

In both instances the causal agent was a vinyl plastic fabric. These plastics are condensation polymers of vinyl acetate and vinyl chloride. The latter substances have been known to be sensitizers and primary irritants. The finished polymers have been regarded as innocuous.

Bauer,[1] Greenfield,[2] Levin and Behrman,[3] Zakon[4] and Zeisler[5] reported contact dermatitis caused by wrist watch straps, garters and suspenders made of "elastiglass," a vinyl acetate and chloride polymerization product. The dermatitis in these cases was ascribed to traces of the plasticizer or stabilizer (dibutyl tin maleate or dibutyl sebacate) not properly removed during the production of the "elastiglass."

Workers engaged in coating fabrics with the copolymer of vinyl chloride and vinyl acetate acquired a dermatitis which was avoided when the incidental formation of biacetyl had been eliminated.[6]

These data show the complexity involved in complete studies of such patients as previously cited. Nevertheless, this report is presented to direct attention to both the clinical and the etiologic features of this type of allergic contact dermatitis.

97 Lincoln Park (5).

1. Bauer, W. W.: Delayed Appearance of Reaction to Elastiglass Wrist Watch Strap, J. A. M. A. **116**:404 (Feb. 1) 1941.

2. Greenfield, I.: Elastiglass Dermatitis from Wrist-Band, Urol. & Cutan. Rev. **46**:120-122 (Feb.) 1942.

3. Levin, O. L., and Behrman, H. T.: Contact Dermatitis from a Plastic Wrist-Band, Indust. Med. **9**:569-570 (Nov.) 1940.

4. Zakon, S. J.: Bullous Dermatitis from Elastiglass, Arch. Dermat. & Syph. **43**:548-549 (March) 1941.

5. Zeisler, E. P.: Dermatitis from Elasti-Glass Garters and Wrist Watch Straps, J. A. M. A. **114**:2540-2542 (June 29) 1940.

6. Schwartz, L.; Tulipan, L., and Peck, S. M.: Occupational Diseases of the Skin, ed. 2, Philadelphia, Lea & Febiger, 1947, p. 475.

TREATMENT OF DERMATOPHYTOSES WITH PROPIONATE-CAPRYLATE MIXTURES

W. C. BREWER, M.D.
GREENCASTLE, PA.

Reports [1] on the use of physiologically compatible fatty acids singly in the treatment of dermatophytoses have been uniformly encouraging. The application

Supplies of the ointment and powder were provided by Wyeth, Incorporated, Philadelphia.

1. Keeney, E. L.; Ajello, L.; Broyles, E. N., and Lankford, E.: Propionate and Undecylenate Ointments in the Treatment of Tinea Pedis and in Vitro Comparison of Their Fungistatic and Antibacterial Effects with Other Ointments, Bull. Johns Hopkins Hosp. **75**:417-439 (Dec.) 1944. Sulzberger, M. D., and Kanof, A.: Undecylenic and Propionic Acids in the Prevention and Treatment of Dermatophytosis, Arch. Dermat. & Syph. **55**:391-395 (March) 1947. Hopkins, J. G.; Fisher, J. K.; Hillegas, A. B.; Ledin, R. B.; Rebell, G. C., and Camp, E.: Fungistatic Agents for Treatment of Dermatophytosis, J. Invest. Dermat. **7**:239-253 (Oct.) 1946. Keeney, E. L.: Sodium Caprylate: A New and Effective Treatment for Moniliasis of the Skin and Mucous Membranes, Bull. Johns Hopkins Hosp. **78**:333-339 (June) 1946.

of fatty acids to dermatophytoses stems from the work of Peck and others.[2] These authors found that concentrated sweat, by virtue of its propionic and caprylic acid content, is an efficient fungistatic agent and that preparations of these acids and their salts are effective clinically. Peck and Russ [3] found a combination of propionates and caprylates to be more effective than either one alone, and their series of 124 treated patients established the fact that these compounds were exceptionally well tolerated. Therefore, propionate-caprylate ointment (ointment "sopronol" propionate-caprylates compound, a water-soluble ointment containing 12.3 per cent sodium propionate, 2.7 per cent propionic acid, 10 per cent sodium caprylate, 5 per cent zinc caprylate and 0.1 per cent dioctyl sodium sulfosuccinate) and powder (powder "sopronol" propionates-caprylate compound, a dusting powder containing 15 per cent calcium propionate, 5 per cent zinc propionate, 5 per cent zinc caprylate and 0.25 per cent propionic acid in a talc base) were chosen for evaluation in the patients described in this brief clinical report.[4]

MATERIAL AND METHODS

The present series consisted of 39 patients seen in private practice, ranging in age from 6 months to 57 years. Each had a positive smear for dermatophytes.

TABLE 1.—*Agents Used in Previous Treatment*

Agents	No. of Cases
None	22
Undecylenic acid	4
Undecylenic acid, salicylic acid and potassium permanganate	2
Undecylenic acid, potassium permanganate and ultraviolet rays	1
Potassium permanganate	1
Iodine	5
Iodine and glycerin	1
Iodine and potassium permanganate	3

The duration of symptoms varied from a week to ten years, but in most cases it was a month or less. Table 1 shows the agents used in the previous treatment of 17 patients in the series.

Table 2 summarizes the presenting signs and symptoms at the time of the first examination. It will be noted that erythema and pain were uniformly observed, with pruritus and discoloration present in the great majority of cases.

Twelve of the cases were graded as severe, 23 as moderate and 4 as mild. The toes were invariably involved. The lesions extended onto the plantar surface in 29 cases and onto the dorsal surface in 19. Trichophytid areas were found in 7 patients. Six of these had been treated previously with undecylenic acid, potassium permanganate or iodine or a combination of agents.

2. Peck, S. M.; Rosenfeld, H.; Leifer, W., and Bierman, W.: The Role of Sweat as a Fungicide, with Special Reference to the Use of Constituents of Sweat in the Therapy of Fungous Infections, Arch. Dermat. & Syph. **39**:126-146 (Jan.) 1939.

3. Peck, S. M., and Russ, W. R.: Propionate-Caprylate Mixtures in the Treatment of Dermatomycoses, with a Review of Fatty Acid Therapy in General, Arch. Dermat. & Syph. **56**:601-613 (Nov.) 1947.

The simplest possible plan of treatment was adopted in order to insure cooperation by the patients. Propionate-caprylate ointment was applied to the lesions twice daily, and propionate-caprylate powder was used in stockings and shoes.

RESULTS

All lesions healed in periods ranging from seven to twenty days, with an average of 13.6 days. Lesions were considered healed after the disappearance of inflammation, vesicles, bullae, maceration or scaling. There was not a strict correlation between length of mycotic infection and healing time, although the trend was in the direction of the longer the infection, the longer the healing time. The newly formed skin was still thin, somewhat hyperemic and doubtless subject to renewed mycotic infection. For this reason treatment was continued four weeks after healing. (In 2 cases the follow-up treatment lasted only a week.)

None of the patients complained of irritation, and there was no evidence of sensitization. On the contrary, preexisting "id" areas disappeared during treatment. There were no recurrences of infection during the period of observation (four to six months in most cases).

TABLE 2.—*Presenting Signs and Symptoms*

Symptom	No. of Patients
Erythema	39
Pain	39
Pruritus	36
Discoloration	35
Fissures	25
Scaling	22
Edema	21
Exudate	18
Vesiculation	17

COMMENT

In the past, treatment of dermatophytoses had fallen into two categories. Either the treatment was ineffective, as with boric acid, or it was so violent as to superimpose another dermatitis, inducing "id" areas (owing to absorption of mycotic debris). The skin of patients who are subject to mycotic infection is likely to be thin, as it was in 36 cases in this series. Such patients require bland medication.

The propionate-caprylate mixtures fill a real need. In this series of 39 patients they were very effective and yet caused neither irritation nor sensitization.

SUMMARY

Thirty-nine patients with dermatophytosis were treated with ointment and powder containing propionates and caprylates. The lesions were healed in an average period of two weeks. This result is highly significant in view of the fact that 25 of these patients exhibited fissures at the beginning of treatment.

There were no undesirable reactions.

Based on this series of 39 patients, the conclusion is reached that propionate-caprylate treatment of dermatophytoses is eminently effective.

Correspondence

ARTERIOSCLEROSIS OBLITERANS AS A CAUSE OF ULCERS OF THE LEG

To the Editor:—I have read the paper on "Arteriosclerosis Obliterans as a Cause of Ulcers of the Leg," by Shapiro and Nomland, in the ARCHIVES of January 1950, with great interest. Arterial disease is clearly a more important factor in the etiology of these ulcers than is generally recognized.

May I draw your attention to the pioneer work of John Gay on this subject, which has been sadly neglected? In the "Lettsomian Lectures of 1867," published in London by Churchill in 1868, and with the title of "On Varicose Diseases of the Lower Extremities," he described the results of his investigations on ulcers of the leg based on clinical observation and careful dissection. He stated (p. 161): "I distinguish three varieties of ulcer—the simple, venous and arterial." He described these types and the pathologic changes in the vessels found on dissection both at operation and autopsy. In a summary he said, "The arterial ulcer, generally without bronzing, but with induration of the tegument, and due to incompetency of the arteries, through disease of their coat. In some cases, however, the morbid changes which characterize the second and third classes are conjoined."

The whole of his work on this subject is well worth reading by those interested in the subject, and much can be learned from it.

I have written this note to you because I feel John Gay deserves recognition even though posthumous.

S. T. ANNING, M.D., M.R.C.P., Leeds, England.

News and Comment

GENERAL NEWS

The Osborne Fellowship in Dermal Pathology.—The American Academy of Dermatology and Syphilology established at its annual meeting on Dec. 7, 1949, The Earl D. Osborne Fellowship in Dermal Pathology. The purpose of this Fellowship is to provide annually for one year the opportunity for study and training in dermal pathology to a postgraduate student who has completed satisfactorily at least two years of training in dermatology or one of its allied branches, in accordance with the requirements of the American Board of Dermatology and Syphilology. A stipend of $1,000 will be given to the candidate selected. The period of training will be spent at the Armed Forces Institute of Pathology, Washington, D. C., the appointment being subject to approval by the Director of the Institute. As the American Board of Dermatology and Syphilology has approved the Institute for one year of training, the time spent will be accredited by the Board. The primary purpose of this Fellowship is to train dermal pathologists. The large amount of material in dermal pathology at the Institute will be available for study, and, under special circumstances and with approval, original research may be undertaken under the direction of the chief of the dermal pathology section of the Institute.

Dermatologists in training who are interested may obtain application blanks for the Earl D. Osborne Fellowship from Dr. Hamilton Montgomery, Mayo Clinic, Rochester, Minn., Chairman of the Committee on Pathology of the American Academy of Dermatology and Syphilology. The first appointment will become effective approximately Oct. 1, 1950.

British Association of Dermatology and Syphilology.—The Annual General Meeting of The British Association of Dermatology and Syphilology will be held in Edinburgh, Scotland, on July 13, 14 and 15, 1950. The principal subject for discussion will be "The Endocrines in Dermatology." The "Pemphigoid Dermatoses" will also be discussed. Dermatologists from the United States and elsewhere will be welcome at this meeting.

Society Transactions

BRONX DERMATOLOGICAL SOCIETY

Arthur Sayer, M.D., *President*

Henry Silver, M.D., *Secretary*

Oct. 21, 1948

Mycosis Fungoides Treated Successfully with Ethylstibamine (Neostibosan®). Presented by DR. MAX BERKOVSKY.

E. T., aged 56, an iron worker of German descent, was first seen by me in March 1948. He stated that the eruption appeared in August on the upper extremities and gradually spread, involving the entire body. It was resistant to local therapy.

The patient was well nourished and presented a generalized eruption consisting of dry and oozing purplish patches which varied in size and did not show any definite pattern of distribution. The most outstanding feature was the intense pruritus. There was generalized adenopathy present. The liver and spleen were not enlarged.

The Wassermann reaction of the blood was negative. Examination of the urine showed no abnormalities. Examination of the blood showed a normal count except for a 10 per cent eosinophil count. Histologic examination of a lesion taken from the back was made by Dr. Charles F. Sims. The pathologic findings were compatible with a diagnosis of mycosis fungoides.

Roentgen ray treatment, in weekly doses of 75 r, for a total of 300 r, was given to different areas without appreciable improvement. Treatment with ethylstibamine (neostibosan®) was then instituted. The patient received weekly intravenous injections, and after the third injection some lesions began to undergo involution. At the same time the itching diminished considerably. After a course of ten weekly injections all the lesions cleared. Treatment with the antimony preparation was concluded in June, and there followed weekly injections of crude liver extract. About the middle of August a few new lesions appeared, accompanied with mild itching. After the initial injection of ethylstibamine the new lesions disappeared and the itching ceased. The patient has received eight injections of the antimony preparation during the second course, and there has been no further relapse.

DISCUSSION

DR. JOHN GARB: Dr. Berkovsky used ethylstibamine in the treatment of his patient, while my experience has been with antimony potassium tartrate (tartar emetic, stibophen (fuadin®) and "stibanose" (the diethylaminoethanol salt of sodium antimony gluconate). "Stibanose," like ethylstibamine, contains pentavalent antimony and is less toxic.

I have so far treated 10 patients with mycosis fungoides, diagnosed clinically as well as histologically, at the New York Skin and Cancer Hospital. The duration of the disease varied from six months to seventeen years. For 3 of these patients the drug acted almost as a specific. The first patient treated has been in excellent health, free of lesions and subjective symptoms for the past eighteen months. The second patient, with infiltrative patches, nodular lesions and a tumorous growth of six months' duration, experienced considerable relief from itching after one injection of 5 cc. of 1 per cent antimony potassium tartrate and a noticeable regression of

the lesions after the third injection. This patient was entirely free from lesions after May 1948. The third patient had lesions of fifteen years' duration. After only two injections of 1 per cent antimony potassium tartrate, for a total of 7.5 cc., the lesions had already shown signs of undergoing involution. After sixteen injections all the lesions had completely regressed except for the superficial scaly patches on the abdomen and thighs. The injections were discontinued because of myocardial changes demonstrated clinically and by electrocardiographic tracings. Recent examination showed evidence of recurrent lesions.

The recurrences may rightly be attributed to insufficient treatment. Injection with antimony preparations, therefore, should be continued once weekly for six months for all patients with mycosis fungoides who are clear or almost clear of lesions. Of the remaining 7 patients, 1 acquired a drug eruption to antimony, 4 responded either partially or poorly and 2 died.

To my great surprise I recently came across references in the literature to the previous use of antimony potassium tartrate in mycosis fungoides. Two patients were presented by Dr. Reeves (ARCH. DERMAT. & SYPH. **22**:349-352 [Aug.] 1930) at the St. Louis Dermatological Society and 2 by Dr. Shaw (ARCH. DERMAT. & SYPH. **23**:1182-1183 [June] 1931) at the Dermatological Conference of the Mississippi Valley from the Barnard Free Skin and Cancer Hospital. The patients of Dr. Reeves showed initially encouraging results, but those of Dr. Shaw showed only slight improvement.

DR. DAVID BLOOM: In a patient under my care, a woman aged 70 with mycosis fungoides of plaque and tumor formation, I observed remarkable regression of a large tumor and simultaneous disappearance of the infiltration of the plaques following administration of stibophen. After fifty-five injections, treatment with stibophen was discontinued because new lesions appeared during the course. There is no doubt that antimony preparations are a valuable adjuvant, but they by no means have curative effect.

DR. RUDOLF L. BAER: It is difficult to discuss diagnosis in this case, now that the eruption has disappeared; however, on the basis of the remnants of the eruption seen tonight I should like to ask whether the possibility of dermatitis herpetiformis was considered. The 10 per cent eosinophil count and the failure of response to roentgen therapy would more likely be associated with dermatitis herpetiformis than with mycosis fungoides. Also, if this is a case of dermatitis herpetiformis the good response to antimony would be most interesting. Pharmacologically antimony and arsenic are closely related, and it would not be surprising if the two diseases, both of which respond to arsenic in some cases, would similarly respond to antimony.

DR. LOUIS CHARGIN: As Dr. Baer said, at this time it is difficult to make a diagnosis of mycosis fungoides. The picture now suggests the end stage of multiform erythema. There can be no question of the remarkable efficacy of the antimonials in mycosis fungoides, but apparently this is only a temporary measure, comparable to what has been experienced with gold in lupus erythematosus. In the latter, remarkable effects are at times achieved, but gold therapy cannot be continued indefinitely even if the disease responds. The same principle applies to antimony in mycosis fungoides. I think both therapies are not without danger and must be used cautiously.

DR. FRANK E. CROSS: Is antimony more toxic in mycosis fungoides than in granuloma inguinale? In my many years of experience of treating granuloma inguinale with antimony potassium tartrate, aside from sclerosis of the veins and occasional nausea and vomiting, I have never seen the severe reactions that Dr. Garb mentions. I should also like to ask Dr. Garb whether his patient died as a result of the disease or whether the treatment was a contributory factor.

DR. CHARLES F. SIMS: Over how long a period did Dr. Garb continuously use the antimony preparation?

DR. HENRY SILVER: I had the opportunity to see the patient before treatment with ethylstibamine was instituted. There were no lesions suggestive of dermatitis herpetiformis or erythema multiforme. The clinical features suggested early mycosis fungoides. Frankly, I cannot see how one can make a diagnosis from the few remaining lesions. My clinical judgment was corroborated by Dr. Sims's pathologic report.

DR. JOHN GARB: It is known that antimony is a toxic drug, particularly for the myocardium. Three to six weeks after the treatments have been discontinued the electrocardiogram usually reverts to normal.

It is too early to state with certainty, because of the small series of cases, but it seems to me that a greater percentage of patients with mycosis fungoides have serious disturbances affecting the heart than a corresponding age group in the general population. It may be that lesions of mycosis fungoides sometimes involve or may even cause a particular disease of the heart, in which case the use of antimony preparations may prove beneficial.

In answer to Dr. Sims's question, the first patient treated has been receiving antimony preparations since April 1947. She is still receiving stibophen twice weekly for the residual patches. The report of this case was recently published *J. Invest. Dermat.* **10**:43-48 [Feb.] 1949).

In answer to Dr. Cross, the patient who died recently showed encouraging results at first but acquired bacterial endocarditis and other serious complications. The observations at autopsy will be detailed in a paper to be submitted shortly for publication. The second patient who died, a woman aged 62, had coronary heart disease before treatment with the antimony compound was started. This patient likewise had improvement at the beginning, with diminution of the itching and regression of some of the nodular and infiltrative lesions. She died of cardiovascular and renal complications.

DR. MAX BERKOVSKY: I wish to reiterate what Dr. Silver said concerning the diagnosis. The case was one of mycosis fungoides. One should not be misguided by the eosinophilia in making a diagnosis of dermatitis herpetiformis, because the amount of itching explains the high eosinophil count.

Ragweed Dermatitis: Oral Hyposensitization. Presented by DR. ALEXANDER A. FISHER.

S. L., aged 45, resident of Sullivan County, N. Y., is a patient at the New York Skin and Cancer Hospital. He has had a recurrent eruption for the past six years.

For four years the eruption began in the middle of August and subsided about six weeks later with the onset of the first spell of cold weather. In 1947 the eruption began in July and lasted until the first frost. At the time of writing in 1948, the eruption has lasted four weeks longer than during any previous year.

The eruption involves the face, forearms, legs and scrotum. It is dry and lichenified.

Oral hyposensitization with ragweed oleoresins was begun last week. Ragweed and pyrethrum gave positive reactions on patch tests.

Ragweed Dermatitis: Oral Hyposensitization. Presented by DR. ALEXANDER A. FISHER.

P. B., a man aged 66, was presented before this society in November 1946 with a perennial ragweed dermatitis of twelve years' duration, with exacerbations in September.

In April 1946 oral hyposensitization was begun. During 1946 there was slight, if any, improvement. During 1947, there was slight improvement, and the usual exacerbation in September was not as severe as usual. In 1948 the patient was entirely free from the eruption from February until the beginning of September. During that month there was a mild flare-up. There was about 75 per cent improvement of the condition in 1948 as contrasted with previous years.

DISCUSSION OF CASES OF RAGWEED DERMATITIS

DR. MORRIS LEIDER: This is an eczematous contact type dermatitis in no essential way differing from the dermatitis caused by the ivy plant or nail polish, for example. Ragweed dermatitis is not related to atopy. The allergen involved is not the protein fraction, as in atopy of seasonal rhinitis and asthma, but is an oleoresin extracted by lipid solvents. It is comparable to the oleoresins of ivy, sumac, oak and pyrethrum, for example. The cutaneous distribution of ragweed dermatitis is notable because it is classic for an airborne allergen. The involvement is of the exposed portions of the skin and such covered portions as may be reached by the chimney effect of sleeves, trousers and skirts. Such clothes create a virtual draught which mechanically wafts an airborne allergen onto apparently protected sites. The oleoresin of ragweed must have a lower sensitizing potential than that of ivy. This situation may exist because the content of oleoresin in pollen is minute and, though it may be greater in the plant itself, contact with the ragweed plant is less common than that with the ivy plant except in agricultural occupations. In any event, everyone receives ragweed pollen on the skin seasonally and regularly, but few become sensitized; whereas perhaps 60 to 70 per cent of those who come into contact with poison ivy even once become sensitized.

The mechanism of hyposensitization by oral administration of the allergen is not clear. In the case of allergic states that are characterized by antibodies, particularly by neutralizing or blocking antibodies, more reasonable explanations can be offered for the apparent benefit. But in allergic eczematous contact type dermatitis, the existence of antibodies is unknown and any explanation of the beneficial effect of administering an eczematogenic allergen is unsubstantiated.

DR. RUDOLF L. BAER: Dr. Howell advised me that Dr. Shelmire and he believe that in ragweed dermatitis the original sensitization does not occur by exposure to the pollens through the air. For sensitization to take place, a more massive exposure, i. e., contact with the weed itself, is necessary. An exposure to the airborne quantities of pollens is adequate for eliciting a reaction only in those highly sensitive. This may explain the fact that one rarely sees cases of ragweed dermatitis in New Yorkers who are not directly exposed to the weed. It is interesting to note that the side effects from the type of oral hyposensitization used by Dr. Fisher are exactly the same as those Dr. Peck mentioned as occurring during penicillin hyposensitization, i. e., flare-ups of old sites of dermatitis, vescular eruptions of the hands and gastrointestinal upsets, for example. I should like to ask Dr. Fisher whether his patients were tested with the protein fraction of the pollen.

DR. SAMUEL M. PECK: Do these patients show immediate reactions to the other fractions?

DR. ARTHUR SAYER: I have observed definite sensitivity to the oil fraction of ragweed proved by patch tests. The eruption is commonly erythematous and scaly, affects the face, appears at the onset of ragweed pollination and recurs on yearly exposure. It disappears when the ragweed season terminates, without immunization therapy.

DR. DAVID BLOOM: Do these patients present reactions of the mucous membranes similar to those observed in hay fever?

DR. ALEXANDER A. FISHER: In answer to Dr. Peck, these patients show no immediate reaction to scratch or intradermal tests with the protein fraction. They are sensitive only to the oleoresin in patch test. They do not have ragweed hay fever as a rule, and, if they do, the occurrence is merely a coincidence.

Twelve patients with ragweed dermatitis under my observation reacted to patch tests with pyrethrum as well as with ragweed oleoresin. One can acquire ragweed dermatitis in New York city since there are ragweed plants in our parks and in many empty lots. Most of the patients, however, are farmers or persons who reside in the suburbs, especially in Queens County. The sensitivity may be acquired by direct contact with the plants, in which case the eruption in the beginning is likely to be vesicular and is often confused with poison ivy dermatitis. On the other hand, the contact may be from airborne pollen to which enough oleoresin clings to affect the sensitive person.

The material used for treatment was obtained from the Graham Laboratory, Willow Lane, Dallas, Texas. It comes in three strengths, the oleoresin being diluted respectively 25, 50 or 100 times with corn oil. The patient takes 1 drop in a capsule orally and gradually increases the number of drops. One patient could not tolerate the treatment because of severe gastrointestinal symptoms which followed his taking 1 drop. All the others tolerated the medication even when eruptions developed. In that event medication was discontinued for a day or two and then resumed with a smaller dose, which as a rule was well tolerated. One has to be extremely patient with this form of treatment since several of the patients get no appreciable relief until treatment has been given for two years. The maintenance dose was 12 drops twice weekly of the 1:25 solution, given all year round.

Neurodermatitis Treated with Resin of Podophyllum. Presented by DR. JOHN GARB.

A. T., a woman aged 39, has been troubled for the past fifteen months with an eruption of the thighs associated with moderately severe pruritus. Her maternal grandmother and a cousin had asthma.

On the inner surface of each thigh there was a large, uniform erythematous and excoriated patch, more extensive on the right. The lesions were well defined and consisted of closely aggregated, lichenified, somewhat shiny papules ranging in size from that of a pinhead to that of a match head. The itching was slight at first but increased in intensity as the patches enlarged, and after bathing.

The Wassermann and Kahn reactions of the blood were negative. Examination of the urine showed no abnormalities.

Nine weekly superficial roentgen ray exposures, 75 r each, were given to the right thigh from Aug. 3 until Oct. 14, 1948, for a total of 675 r. The left thigh was treated during the same period with weekly applications of an ointment containing 2.5 per cent of resin of podophyllum and later with a strength varying from 5 to 7.5 per cent. The ointment was covered with waxed paper and a layer of gauze and bandaged. The patient was advised to remove the bandage after two days and apply a mild soothing ointment. The normal skin was protected with flexible collodion for an inch (2.5 cm.) beyond the borders of the lesions.

After three weeks the itching almost completely abated. On September 8, after four treatments, the lesions on both thighs had considerably regressed. The treatments were continued until the residual patches completely underwent involution.

Reexamination of the patient on October 20 showed a slight recurrence on the upper part of the patch on the right side treated with roentgen rays. There is no recurrence on the left side treated with resin of podophyllum.

DISCUSSION

DR. NATHAN SOBEL: The result obtained by Dr. Garb is excellent and compares favorably with that following painting with crude coal tar. With regard to this seemingly objective method of comparative testing of a drug, our experience with roentgen rays in the treatment of acne is pertinent. It is known that treating one side only with the ray often benefits the other side as well. Is there a similar action in this case, in which the benefit obtained from roentgen rays applied to one thigh also benefited the opposite site?

DR. HANS H. BIBERSTEIN: It cannot be doubted that the result is conspicuously satisfactory. The question is, how was it accomplished? Since one can obtain good results by the use of other peeling procedures, I can imagine that the destructive and at the same time stimulating action of resin of podophyllum can have a beneficial effect on the renewal of the skin. It would be of interest to follow the action histologically.

DR. MAURICE UMANSKY: The action of resin of podophyllum in acuminate condylomas is said to be due to constriction of the vessels underneath the growths (Culp and Kaplan, "1944 Yearbook of Dermatology"). Would the same apply to neurodermatitis?

DR. HENRY SILVER: Dr. Umansky seems to be under the impression that the action of resin of podophyllum is confined to the blood vessels. I cannot agree with that. Sullivan and King (ARCH. DERMAT. & SYPH. **56**:30-47 [July] 1947) showed that resin of podophyllum has a cellular action and that is why some persons have attempted to try resin of podophyllum in treatment of early or superficial epithelioma with satisfactory results.

DR. JOHN GARB: As to the question raised by Dr. Sobel, it was Dr. Niles who did these experiments on acne (ARCH. DERMAT. & SYPH. **27**:89-100 [Jan.] 1933). Even if the roentgen rays had an indirect effect, the result of treatment of the left thigh seems to be far superior to that of the right thigh, which received roentgen rays alone and is showing signs of recurrence.

Much more striking is the result obtained with resin of podophyllum in treatment of a man aged 27, who had neurodermatitis of the legs accompanied by severe itching for a period of ten years. One application of 10 per cent resin of podophyllum in an ointment base to the right leg showed a greater therapeutic effect two weeks later than administration of roentgen rays (eight weekly exposures, 75 r each) to the left leg did two months later. In another patient with lichen chronicus simplex of fifteen years' duration an unusually good result was obtained with resin of podophyllum ointment. I have used various concentrations of resin of podophyllum in ointment base, in 70 per cent alcohol and in compound tincture of benzoin, the choice depending on the case, location and the thickness of the lesions.

In neurodermatitis of the eyelids one has to be particularly careful to prevent inflammation of the eyes. The safest and best procedure seems to be application of 1 to 2 per cent of resin of podophyllum in compound tincture of benzoin or 70 per cent alcohol.

A Case for Diagnosis (Pustular Psoriasis? Acrodermatitis Perstans?). Presented by DR. ADOLPH ROSTENBERG and DR. WILLIAM M. SISKIND.

A Case for Diagnosis (Poikiloderma Vasculare Atrophicans?) with Psoriasiform Lesions on Palms, Soles and Scalp. Presented by DR. DAVID BLOOM.

Circumscribed Myxedema of the Legs, Associated with Hyperthyroidism. Presented by DR. ELLEN REINER.

Pyoderma Chancriforme Faciei: Epithelioma? Syphilis? Presented by DR. NATHAN SOBEL.

Condom Dermatitis of the Genital Areas. Presented by DR. MAURICE UMANSKY.

CHICAGO DERMATOLOGICAL SOCIETY

S. W. Becker, M.D., *President*

Leonard F. Weber, M.D., Secretary

Oct. 20, 1948

A Case for Diagnosis (Generalized Erythema in a 5 Month Old Infant). Presented by DR. D. V. OMENS and (by invitation) DR. HAROLD D. OMENS and DR. S. BARSKY.

DISCUSSION

DR. CARL W. LAYMON, Minneapolis: There are several features about this case which suggest a diagnosis of ichthyosiform erythroderma: the fact that the eruption was present at birth, the presence of erythema, the generalized exfoliation, the bullae and the fact that the flexor surfaces were maximally involved. These are all features which are not found in ordinary ichthyosis vulgaris. The latter disorder is never present during the first few days of life.

Adenoma Sebaceum (Pringle's Disease) in a 4 Year Old White Boy, with Convulsions. Presented by DR. D. V. OMENS and (by invitation) DR. HAROLD D. OMENS and DR. D. MUSGRAVE.

Tuberous Sclerosis Associated with Adenoma Sebaceum (Pringle Type) in a 17 Year Old Girl. Presented (by invitation) by DR. EDWARD L. LADEN.

DISCUSSION

DR. MAURICE OPPENHEIM: Both cases could be considered as formes frustes of von Recklinghausen's disease. The second patient had also nevi and fibromas of the body, as a proof that Recklinghausen's disease and Pringle's disease are connected. And another proof is provided by the presence of neurologic symptoms in the 2 cases.

DR. STEPHEN ROTHMAN: I am sorry that I have to disagree with Dr. Oppenheim and with the general tendency for the Pringle type of adenoma sebaceum to be regarded as a manifestation of Recklinghausen's disease. In Recklinghausen's disease there is no adenoma sebaceum and no tuberous sclerosis. In Pringle's adenoma sebaceum café au lait spots do not occur and the fibromas are not neurofibromas. The inheritance of the two conditions does not run in the same families.

Generalized Progressive Scleroderma (Acrosclerosis) in a Woman of 66. Presented by DR. THEODORE CORNBLEET and (by invitation) DR. DAVID COHEN and DR. D. MUSGRAVE (by invitation).

Generalized Progressive Scleroderma (Acrosclerosis) in a Woman of 64. Presented by DR. THEODORE CORNBLEET and (by invitation) DR. H. SCHORR and DR. D. MUSGRAVE.

Generalized Progressive Scleroderma in a Negro Woman Aged 18, with Involvement of Face, Trunk and Extremities. Presented by DR. F. E. SENEAR and STAFF.

DISCUSSION

DR. CARL W. LAYMON, Minneapolis: In the past there have been many discussions before the society regarding the exact relation between acrosclerosis and diffuse scleroderma. In my opinion both are variants of the same pathologic process. Acrosclerosis is a form of diffuse scleroderma in which vasomotor symptoms predominate and in which the process does not become generalized but remains localized to the extremities and face. I should like to mention that we have seen 4 cases of acrosclerosis in which there were telangiectatic lesions on the face. This may prove to be a helpful diagnostic sign in differentiating acrosclerosis from ordinary scleroderma.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: Various forms of vasomotor disturbances occur in association with generalized scleroderma. In acrosclerosis, the scleroderma occurs peripherally first of all in the hands and face and in almost every instance it is preceded by Raynaud's symptoms for months or years. Usually this situation does not exist in the so-called diffuse generalized scleroderma. I believe the difference is more of degree than of kind. The treatment of acrosclerosis by sympathetic resection has proved disappointing; the Raynaud's symptoms are checked, but the sclerosis often progresses. There is no direct approach to treatment. The patient is most comfortable in a warm atmosphere, with treatment with systematic measures of physical therapy and the use of mild antispasmodic drugs such as physostigmine.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I wish to emphasize certain pathologic aspects regarding forms of scleroderma. There is confusion in the literature regarding scleroderma and dermatomyositis. The Mt. Sinai group of physicians would place lupus erythematosus in with the other two conditions because of fibrinoid changes and alteration of the collagen. In my experience, changes in the collagen in the skin are minimal and hyaline and fibrinoid changes in the capillaries occur very infrequently. In acrosclerosis and in either localized or generalized scleroderma, there are obliterative changes in the vessels not only in the skin but also in the muscles of the diaphragm and the heart, as well as shortening of the esophagus. Obliterative changes in the vessels are not seen early in acrosclerosis when the phenomenon of Raynaud's disease predominates. I am in accord with the Mt. Sinai group that scleroderma is a collagenous disease, but there are also changes in the vessels, and the changes in the collagen may be secondary to the obliterative changes in the vessels, which by shutting off the circulation cause atrophy and homogenization of the collagen. This hypothesis accounts for the hyaline changes in the muscles in scleroderma as contrasted with the parenchymatous degeneration seen in dermatomyositis. One sees quite a few cases of acrosclerosis in which there is progression to a certain point and then involution. One may see cases of superficial scleroderma with or without sclerodactylia that have been mistaken for Addison's disease because of the low blood pressure and excessive melanin pigmentation. At the Mayo Clinic we have not been seeing recently the severe forms of generalized scleroderma which usually have a fatal outcome and which we used to see many years ago.

DR. THEODORE CORNBLEET: In the 2 patients with so-called acrosclerosis there were deposits of calcium and this in the face of the fact that the blood calcium level was within the normal range in 1 patient, and below it in the other. These are not unusual occurrences. Yet the idea is held, that this disorder is due to hyperparathyroidism, and surgical intervention is employed on that basis. The blood calcium level denies this. Curiously enough, the patient improves after partial parathyroidectomy. Unfortunately, this betterment is temporary only.

Lichen Planus Associated with Turner's Syndrome. Presented by DR. JAMES R. WEBSTER and DR. THEODORE CORNBLEET and (by invitation) DR. D. MUSGRAVE.

G. G., a Negro woman aged 24, has a generalized pruritic skin eruption of two months' duration. The patient is 4 feet 2 inches (127 cm.) tall, has cubitus valgus and presents several congenital anomalies together with absence of secondary sex characteristics. She has never menstruated.

On examination there are seen to be infantile development of the breasts, absence of pubic hair and webbing of the neck. The ring fingers of both hands are the same length as the little fingers. There is a generalized flat-topped, papulosquamous eruption most pronounced over the back, buttocks, chest and abdomen. No plantar or palmar lesions are seen, and the face is only slightly involved. In some areas the lesions have become confluent.

Generalized Lichen Planus and Fixed Drug Eruption Due to Sulfathiazole. Presented by DR. THEODORE CORNBLEET and (by invitation) DR. H. SCHORR and DR. D. MUSGRAVE.

Lichen Planus. Presented by DR. C. W. FINNERUD and (by invitation) DR. J. M. RIDDELL.

DISCUSSION

DR. THEODORE CORNBLEET: Turner's syndrome was first described in 1937. It has been noted by other observers. E. P. Sharpey-Schafer reported a case with postmortem observations in the *Lancet* for 1941 (*Lancet* **2**:559-560 [Nov. 8] 1941). The three characteristic features are the webbing of the neck, which here is perfectly typical, running from the mastoid region down to the acromion process; the cubitus valgus, and the infantilism. The distinction here should be made between pituitary disorders, and I think that can be done fairly well. The urinary excretion of 17-ketosteroids was within normal limits. Estrogens were not present. The presence of some pubic and axillary hair speaks against the pituitary syndrome and in favor of an ovarian insufficiency. In the case of Sharpey-Schafer a postmortem examination was made. All the glands of internal secretion were found normal, but the ovaries could not be found. In addition, there was a tuberculous involvement of the region where the ovary should be.

In the patient with the combination of lichen planus and fixed drug eruption, the administration of sulfathiazole produced a reddening of the dark areas of the fixed drug eruption but did not change the extent or character of the generalized lichen planus eruption. Furthermore the manner in which the lichen planus lesions avoided the sites of fixed drug eruption dramatically pointed away from unity and in favor of duality of cause.

Leukemia Cutis (Aleukemic Type), with Generalized Itching, Ulcer of the Leg and Axillary Adenitis. Presented by DR. JAMES R. WEBSTER and DR. SAMUEL M. BLUEFARB and (by invitation) DR. S. BARSKY.

Lymphoblastoma (Mycosis Fungoides Type). Presented by DR. JAMES H. MITCHELL.

Mrs. McC., aged 53, was first seen on June 18, 1945, with a fungating lesion on the left ramus of the jaw.

Intensive and extensive roentgen ray treatment was continued until March 29, 1947, when intensive treatment was begun with sodium *para*-aminobenzoate. The patient was presented at the April meeting to demonstrate the effectiveness of

that drug. The patient was again presented at the May and June meetings. Gradually there seemed to be a loss of response to the drug, and on May 10, 1948, treatment with it was discontinued and intravenous injections of 1 per cent antimony potassium tartrate in an aqueous solution containing 0.05 Gm. were begun. This treatment has been continued to date and will be continued as indicated.

The patient is again presented to show the excellent results of therapy with injections of antimony potassium tartrate.

Favorable Results of Therapy in Lupus Vulgaris with Combined Calciferol and Streptomycin. Presented by DR. THEODORE CORNBLEET and (by invitation) DR. D. COHEN and DR. D. MUSGRAVE.

Sarcoid in a Negro Boy of 14, with Two Nodules on the Ala Nasi. Presented by DR. MICHAEL H. EBERT and (by invitation) DR. VERA LEAF and DR. D. MUSGRAVE.

Recurrent Acneform and Papulonecrotic Tuberculid Treated Successfully with Streptomycin; Syringocystadenomas. Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. RICHARD B. STOUGHTON.

Tuberculosis Verrucosa Cutis of the Buttock, with Lichen Scrofulosorum. Presented by DR. ARTHUR W. STILLIANS.

Rosacea-like Tuberculid of Lewandowsky; No History or Evidence of Tuberculosis. Presented by DR. CLARK W. FINNERUD and (by invitation) DR. F. J. SZYMANSKI.

A Case for Diagnosis: Leprosy? Sarcoid? Lupus Vulgaris? Presented (by invitation) by DR. F. J. KENDRICK, Gary, Ind.

Sarcoidosis of Skin, Lungs and Nasal Mucosae. Presented (by invitation) by DR. SHELDON A. WALKER and DR. EDWARD L. LADEN.

Xanthoma Tuberosum Multiplex. Presented by DR. THEODORE CORNBLEET and (by invitation) DR. H. SCHORR and DR. S. BARSKY.

A Case for Diagnosis (Lichenoid Tuberculids of Ankles?). Presented by DR. MICHAEL H. EBERT and (by invitation) DR. HAROLD M. SPINKA.

A Case for Diagnosis (Lichen Planus of Buccal Mucous Membrane? Leukoplakia? Electrolytic Changes?). Presented by DR. CLEVELAND WHITE.

Epidermolysis Bullosa, Dystrophic Form, with Porphyrinuria, in a 17 Month Old White Infant. Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. FREDERICK V. HAUSER.

A Case for Diagnosis (Epidermolysis Bullosa). Presented (by invitation) by DR. A. BUCHHOLZ.

DISCUSSION

DR. LOUIS A. BRUNSTING, Rochester, Minn.: Porphyrinuria occurs in a number of conditions with fever, diseases of the liver and poliomyelitis and also after the use of alcohol, arsenic and certain other drugs. Porphyrinuria of itself is merely an aggravation of a physiologic state. Porphyria, on the other hand, is an inborn fault of metabolism which may be dormant or become manifest in a variety of ways,

early in life or later. In such cases uroporphyrin is excreted and also porphobilinogen as well as abnormal amounts and kinds of coproporphyrin. The first case is an example of epidermolysis bullosa of the dystrophic type with associated porphyrinuria, not porphyria.

Angioma Serpiginosum? (Telangiectasia Macularis Eruptiva Perstans?). Presented by Dr. Edward A. Oliver and Staff, Veterans Administration Hospital, Hines, Ill.

Trichotillomania in a College Student Aged 22. Presented by Dr. Clark W. Finnerud and (by invitation) Dr. F. J. Szymanski.

Acquired Sebaceous Adenoma with Rhinophyma. Presented by Dr. J. H. Mitchell and (by invitation) Dr. B. Yaffe.

Extensive Pigmented Hairy Nevus. Presented by Dr. James R. Webster and (by invitation) Dr. Francis Hetreed and Dr. Alfred Falk.

Nevus Pigmentosus et Pilosus with Early Leukoderma Acquisitum Centrifugum. Presented by Dr. Francis E. Senear and Staff.

Parapsoriasis (Parakeratosis Variegata? Poikiloderma?). Presented by Dr. Francis E. Senear and Staff.

Neurotic Excoriations in a Schizophrenic. Presented by Dr. Theodore Cornbleet and (by invitation) Dr. D. Cohen and Dr. S. Barsky.

Acrodermatitis Continua of Eight Years' Duration: Successful Treatment with Tobacco Decoction. Presented by Dr. Stephen Rothman and (by invitation) Dr. A. L. Lorincz.

Sister E., a 77 year old nun, was presented before this society by Dr. L. F. Weber in 1942. In the discussion the diagnoses of dermatitis repens, acrodermatitis continua, pustular psoriasis and yeast infection were considered. She appeared at the University of Chicago Clinics on September 9, 1948 because of the severe suppurative dermatitis of the fingertips.

In 1940, after a minor break in the skin of the left thumb, paronychia followed by suppurative dermatitis of the finger tip ensued. Later the process extended to involve all other finger tips. Despite years of many types of treatment, the disease had failed to respond.

Examination revealed absence of all finger nails. The finger tips showed exfoliation, crusting and suppuration over a shiny, red, atrophic base. The ends of the index fingers were slightly conical. Psoriasiform changes were present over both knees and elbows. However, histologic examination of the knee lesion revealed only nonspecific subacute dermatitis. Other nuns were said to show similar changes from frequent kneeling in prayer. Moderate keratolysis exfoliativa was evident on both palms.

Physical examination and laboratory tests were noncontributory. Roentgenograms of the bones of the fingers showed normal conditions. Cultures from the finger tips failed to reveal fungi but the following bacteria were found: aerobic and anaerobic nonhemolytic streptococci, Staphylococcus aureus, Staphylococcus albus, anaerobic staphylococcus and diphtheroids.

Treatment with hot soaks of tobacco decoction for fifteen minutes three times daily was followed by prompt and remarkable recovery.

Photographs before and after treatment, microscopic section of the knee lesion and a photostatic copy of the previous presentation before this society are presented.

Edema of Hands and Feet of an Adult, of Three Months' Duration. Presented by DR. HERBERT RATTNER and (by invitation) DR. H. RODIN and DR. S. BARSKY.

S. W. Becker, M.D., *President*

Leonard F. Weber, M.D., *Secretary*

Nov. 17, 1948

A Case for Diagnosis (Tuberculosis Cutis of the Eyebrow?). Presented by DR. S. ROTHMAN and (by invitation) DR. S. A. WALKER.

ADDENDUM (Jan. 10, 1949).—After presentation, the patient was found to have strongly positive serologic reactions for syphilis. The lesion cleared up promptly under treatment with penicillin after it was refractory to administration of streptomycin. The tentative diagnosis of tertiary (tuberculoid) syphilid was made.

Lichen Nitidus. Presented by DR. JAMES R. WEBSTER and (by invitation) DR. FRANCIS HETREED and DR. ALFRED B. FALK.

J. C., a Negro boy aged 3, presents a papular eruption on the neck, trunk and extremities. The lesions are small and rather uniform and have a grayish hue. Much of the eruption is grouped, and in many areas the papules assume a linear configuration. Itching is minimal. The mother stated that she had noticed the condition for the past three months.

The blood and urine were normal. A roentgenogram of the chest showed normal conditions. A Mantoux test with a dilution of 1 : 10,000 of old tuberculin had negative reactions.

Histologic examination of a lesion on the nape of the neck revealed nests of infiltrate in the papillary layer consisting of round cells, epithelioid cells and an occasional giant cell. The overlying epidermis is thin. The microscopic findings are compatible with a diagnosis of lichen nitidus.

Lichen Nitidus. Presented by DR. D. V. OMENS and (by invitation) DR. H. OMEN and DR. D. MUSGRAVE.

DISCUSSION

DR. THEODORE CORNBLEET: In both patients the Koebner phenomenon was clearly shown. This observation further serves to confound lichen nitidus with lichen planus, though morphologically and clinically only.

DR. JOHN F. MADDEN, St. Paul, Minn.: It has been my feeling that lichen nitidus may be a variant of lichen planus and not associated with tuberculosis.

DR. HENRY E. MICHELSON, Minneapolis: I can state only what Professor Pinkus said: "I saw so many of these little lesions and I started to investigate them and I still do not know what they are."

The microscopic picture, as you know, is fairly uniform. These small granulomas high in the cutis are usually surrounded by epidermis and occasionally contain a few basal cells. I do not believe the condition has anything to do with tuberculosis. Sometimes generalized cases do resemble lichen planus. The disease is of no great consequence. It is merely interesting. If left alone, it tends in time to disappear.

DR. ALFRED B. FALK (by invitation): We at Children's Memorial Hospital were impressed by the linear configuration in our case. Civatte, in 1911, was the first to observe linear grouping of papules along skin folds and furrows of the skin and the confluent type of this condition. In the diffuse type, of which our case is an example, we could find no mention of this observation.

Pityriasis Rubra of Hebra? Presented by DR. S. ROTHMAN and (by invitation) DR. A. L. LORINCZ.

M. W., a 50 year old French housewife with a progressive red scaling skin eruption of twelve years' duration, was previously presented before the Chicago Dermatological Society in October 1941, April 1946 and March 1948. The diagnoses considered in the discussion have been poikiloderma vasculare atrophicans, prefungoid stage of mycosis fungoides, parapsoriasis with ichthyosis, exfoliative erythroderma and lymphoblastoma.

Her eruption commenced as a scarlatiniform erythema which was followed by scaliness appearing successively on the face, neck, thighs, abdomen, chest, scalp and back. Since December 1947 a generalized exfoliative erythroderma with remissions lasting a few days or weeks has been present. During exacerbations, migrating joint pains, generalized stiffness, cutaneous edemas, petechiae, purpura, chills and fever have occurred. Recently scaling increased to 1 pound (0.5 Kg.) daily and extensive erosions appeared.

Family history reveals one sister with arrested tuberculosis and rheumatism.

In July 1946, hysterectomy for squamous cell carcinoma of the cervix was done. There has been no evidence of recurrence to date.

On physical examination the skin showed generalized exfoliative erythroderma, decided atrophy, purpura, hemosiderin deposits and superficial erosions. There was ectropion of both lower eyelids and shedding of the nails. Lymph nodes, liver and spleen were moderately enlarged. Roentgenologic examination of the chest revealed evidence of calcified apical tuberculosis. Extensive hematologic studies including those of the clotting mechanism showed normal conditions except for borderline anemia, increased plasma cells in the sternal marrow and increased capillary fragility. Results of urinalysis were normal except for occasional renal glycosuria. Tests for hepatic and renal function had essentially normal results. Blood chemistry revealed only elevation of plasma globulins, with reversal of the albumin-globulin ratio. Serologic reactions for syphilis were negative. Cultures of the blood yielded no organisms. Cultures of material from the skin showed hemolytic Staphylococcus aureus. Reactions in tuberculin tests were negative in dilutions up to 1 : 10,000.

Biopsy of specimens of lymph node, liver and muscle showed only nonspecific inflammatory changes.

Microscopic section of the skin is presented and shows decidedly atrophic epidermis and subepidermal dense round cell infiltrate continuing downwards to the deep part of the corium as perivascular mantles. The vessel walls are thickened. There is fragmentation of collagen. Deep in the corium extensive hemorrhage is present.

Treatment has been with ultraviolet thorium-X and low dosage roentgen radiation, arsenic preparations, quinine, salicylates, intravenously administered sodium thiosulfate, autohemic injections, calciferol, vitamin K, vitamin A, rutin, ascorbic acid, preparations containing the vitamin B complex, syrup of choline dihydrogen citrate, cystine hydrochloride, ferrous sulfate (feosol®), ketogenic diet, diethylstilbestrol, testosterone and a variety of bland preparations locally applied. Most recently a febrile episode with extended erosions was followed by a remission after

intensive penicillin therapy, administration of progesterone and vitamins and "neohemoplastin" treatment. Treatment with streptomycin and sulfonamides was also tried for short periods without apparent effect.

DISCUSSION

DR. EDWARD A. OLIVER: Some years ago I presented a case as an example of pityriasis rubra of Hebra and was frankly told by a number of men that there was no such condition. At about that time my associates and I were seeing many cases at the Cook County Hospital which we diagnosed as pityriasis rubra of Hebra. After we watched these cases we found that many of them which we had been accustomed to call examples of pityriasis rubra of Hebra became cases of Hodgkin's disease or one of the other lymphoblastomas. Cases of so-called pityriasis rubra of Hebra were somewhat different. In them was presented a diffuse exfoliative dermatitis. The patients complained of extreme cold and of joint pains. The woman shown today had some of these symptoms. I believe this case belongs in the group of poikilodermas and should be investigated along that line.

DR. MAURICE OPPENHEIM: Some authors describe this disease as erythroderma exfoliativa with atrophy. This case is different from other cases of exfoliative erythroderma. Jadassohn published extensive papers about this disease and thought of tuberculosis as the etiologic factor. I believe this case may be simply a precursor of lymphoblastoma, or it might be an early stage of dermatomyositis. There is decided atrophy of the musculature.

DR. THEODORE CORNBLEET: Two points about this patient interested me. First, there was a high level of gamma plasma globulins, and it was said that there was a large number of lymph and plasma cells, too, observed after sternal puncture. These latter cells are the very ones that supposedly furnish gamma globulin and antibodies. Why the above relation should be present in this particular patient remains to be seen. Second, calcifications were found in the lungs. Because of these it might be worth while to think of histoplasmosis.

DR. STEPHEN ROTHMAN: In reply to Dr. Oliver I should like to state that in the past I did not believe in the existence of such an entity either. Also, I noted from the recent paper of Anna Lutz on exfoliative erythroderma that in the Department of Dermatology in Basel not a single case was observed in the course of thirty years which could have been diagnosed as the Hebra or the Wilson type. However, after having observed this patient for seven years, I could not fail to recognize the classically described type of Hebra. This woman displays a severe degree of atrophy and such fragility of the skin that she suffers from extended erosions recurrently. Also, she has pronounced joint pains and episodes of chill and fever, as described by Kaposi. Kaposi mentioned that he observed only 5 or 6 cases in his huge material. Thus, I come to the conclusion that this disease does exist, but is extremely rare.

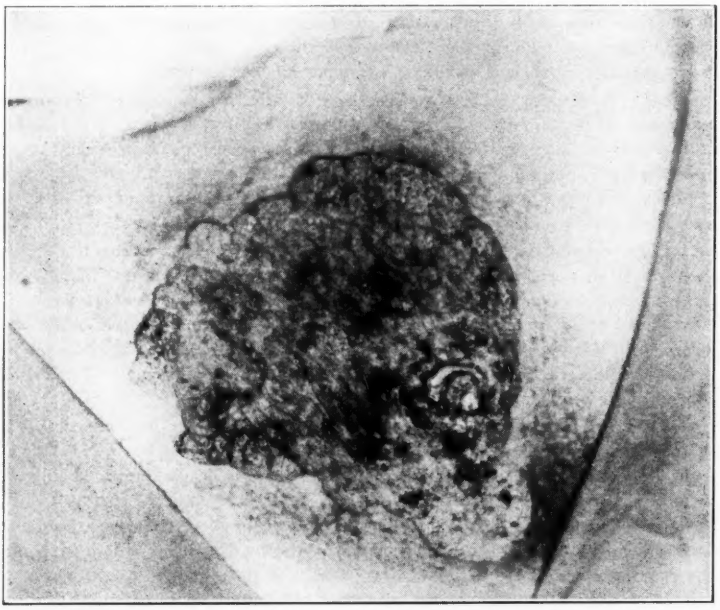
I certainly never saw any exfoliative erythroderma, including the forerunners of lymphoblastomata, which would have shown this frightening degree of atrophy, this poikiloderma-like appearance, this joint involvement and this tendency to cutaneous hemorrhages and, in spite of the gravity of the illness, this chronicity.

For seven years now we have repeatedly performed on the patient all the examinations which modern medicine has invented and have not found lymphoblastoma or any other known systemic disease. It is highly improbable that she has active tuberculosis because her sensitivity to tuberculin is low and her pulmonary lesion was interpreted as a completely calcified healed lesion.

Dr. Cornbleet's points were well taken. The high proportion of gamma globulin obviously means only severe general disease. We shall be glad to follow the suggestion and perform a histoplasmin test.

This patient was presented here by Dr. S. W. Becker in 1941 as having a case of poikiloderma vasculare atrophicans. Indeed, the condition appeared to be that at that time. But we could not find any data on the development of poikiloderma into a generalized exfoliative erythroderma, and, therefore, this diagnosis had to be ruled out.

Intraepidermal Epithelioma (Borst-Jadassohn). Presented by DR. E. A. OLIVER and STAFF, Department of Dermatology, Northwestern University Medical School.



Intraepidermal epithelioma (Borst-Jadassohn type).

Mrs. F. B., a woman aged 75, was first seen by us on May 13, 1948, because of a lesion of thirty years' duration on the outer portion of the upper part of the right thigh. The lesion apparently began as a small erythematous patch which gradually enlarged up to its present size.

No subjective symptoms are present. There are no other similar lesions.

Physical examination revealed no abnormalities except bilateral varicose veins.

Roentgenologic examination of the chest revealed essentially normal conditions. Wassermann and Kahn tests gave negative reactions. Blood count and examination of urine showed no abnormalities.

The patient has had no treatments other than a few suberythema doses of ultraviolet rays and boric acid ointment topically applied. A history of arsenic

ingestion could not be obtained. Until the age of 19 she had lived on a farm in Indiana where both artesian and ordinary well water was obtainable.

Biopsy specimens show the characteristic histologic picture of intraepidermal epithelioma of Borst-Jadassohn.

DISCUSSION

DR. HENRY E. MICHELSON, Minneapolis, Minn.: I think this is a most unusual case, and I wish I had the ability to interpret the microscopic picture to a degree that I would be able to state with certainty that the condition is or is not cancer. I think this case gives one an opportunity to discuss briefly precancerous lesions of the skin. I think that we need to review and probably change our views on the microscopic findings in so-called precancerous lesions. I think there are many lesions with microscopic pictures which are diagnosed as cancer which never become clinical cancer. In this particular section, what impressed me most was the fact that there was no invasion, that, although there was a change in the upper cells, the basal cells were entirely normal, and that there was not a continuation of basal cells back up into the epidermis. The striking change was the variation in the cytologic picture above the basal layer. I felt that the case was not of cancer.

DR. M. R. CARO: I do not believe that there has to be a break through the basal layer before one considers the diagnosis of cancer. I think it is possible to have an intraepidermal epithelioma of either basal or squamous type. In Ormsby and Montgomery's textbook (seventh edition) there is one picture of both in the same section (fig. 360). We have had 2 cases of this type in our collection.

DR. STEPHEN ROTHMAN: I should like to call attention to a possible mechanical factor in the development of this lesion. This woman has worn a girdle which was repeatedly rubbing this area. Chronic mechanical irritation is an extremely common carcinogenic factor.

DR. S. W. BECKER: One of the important things is that the lesion continues to grow for many years. There is no regression such as is seen in lichenified epidermoid lesions. No two pathologists will agree as to what criteria should be used in the diagnosis of carcinoma.

DR. JULIUS GINSBERG: I think there are abnormal mitotic figures to be seen, much more numerous than would be expected in the common wart. There are Bowen-like changes in some cells, and some cells look as though they might change into those characteristic of basal cell epithelioma and others as though they might change into the cells of squamous cell epithelioma. There is no break through the epidermis. This is not necessary. I submitted the section to Dr. Montgomery because it looked identical with the lesion which he had pictured in his textbook. He seemed to feel that this was a Borst-Jadassohn epithelioma if it was an epithelioma. He asked me about the history with regard to arsenicals. I was unable to obtain any history that the patient had taken arsenic in any form, though she had lived in places where she might have been exposed to it.

A Case for Diagnosis (Painful, Persistent Verruca Vulgaris? "Multiple Juvenile Cutaneous Horns? ") in an 8 Year Old Boy. Presented by DR. S. ROTHMAN and (by invitation) DR. E. L. LADEN.

DISCUSSION

DR. M. R. CARO: I thought that histologically this was more of a cutaneous horn than a wart. There was no vacuolar change in the granular layer, and there was no parakeratosis in the scale, both of which characteristics are seen in verruca vulgaris. Histologically there is no basis for a diagnosis of verruca vulgaris.

DR. STEPHEN ROTHMAN: I took the term "multiple juvenile cutaneous horns" from Moncorps' chapter on keratoses in Jadassohn's "Handbuch." Moncorps stated that most authors regard this ailment as a nevoid condition which always starts early in childhood.

A Case for Diagnosis (Nevus, Telangiectatic). Presented by DR. F. E. SENEAR and STAFF.

F. O., a white man aged 19, was admitted for treatment of acne vulgaris and on examination, in addition to acne, was found to have many small telangiectases, scattered and grouped over the face, neck, anterior portion of the chest and upper extremities. These lesions had been present as long as he could remember; they were not increasing in size or number and were asymptomatic.

No other members of the family have a similar condition. There has never been any bleeding from the lesions nor any epistaxis. The mucous membranes are free of lesions. It is of interest that the telangiectases are principally on the exposed surfaces. The Wassermann reaction was negative.

DISCUSSION

DR. STEPHEN ROTHMAN: As it was pointed out, it is indeed remarkable that the telangiectases occur only on the exposed parts. The extensor aspects are much more involved than the flexor surfaces. In 1923 I reported on a case of xeroderma pigmentosum in which test irradiations of the uninvolved skin with ultraviolet rays led to development of gross telangiectases within the sunburned field. I wonder if this case is not due to a similar though incomparably milder light sensitivity in which the primary fault is an innate weakness of blood vessels.

Cutaneous Blastomycosis in a Patient with Pulmonary Tuberculosis. Presented by DR. A. W. STILLIANS.

C. W., a tool grinder aged 31, of slight build, entered the Municipal Tuberculosis Sanitarium on Aug. 1, 1946.

He had been losing weight for eighteen months and coughing for many years. He was found to have far advanced tuberculosis of the upper lobe of one lung. On March 12, 1947, he came to the dermatologic clinic with pustular nodules on the left side of the scalp, the cheeks, the right wrist and the right leg. These had been present for a month. A large mass of granulation covered the distal half of the nose and there was some involvement of the nasal mucous membrane. He complained of pain in both knees, both ankles and the left wrists. In scrapings from the nodules blastomyces were found and a histologic section showed a typical picture for blastomycosis.

He was given 0.015 Gm. of cupric sulfate in dilute citric acid sweetened with saccharin, three times a day. This in a month failed to cause any improvement. Sulfapyridine therapy was tried but caused nausea and vomiting.

On June 18, 1947, after a consultation with the medical staff, he was given 0.4 Gm. of iodine in solution three times a day. Soon after this, improvement was seen in his skin lesions, but he continued to lose weight, and his pulse was rapid. Treatment with iodine was stopped on October 1 and the cupric sulfate solution substituted. Within a few weeks the blastomycosis grew worse and the copper sulfate therapy was stopped. Treatment with sodium iodide was begun, and the skin and nasal lesions were painted daily with tincture of iodine. Improvement soon began, although weight continued to diminish.

On March 15, 1948, treatment with streptomycin was begun, 0.5 Gm. daily until May 26, for a total of 36 Gm. There were no complications due to the drug. The

patient soon began to gain weight, going from a low of 112 pounds (51 Kg.) to his weight at the time of presentation, 133 pounds (60 Kg.)

On April 14 a few nodules were still present on the right cheek but the lesion on the nose was much smaller. Improvement continued slowly until the time of presentation.

On Oct. 30, 1947, his blood contained 82 per cent hemoglobin, 4,720,000 red cells per cubic millimeter and 9,600 leukocytes, with 62.7 per cent neutrophils, 2.7 per cent eosinophils, 13 per cent small lymphocytes, 12 per cent large lymphocytes and 11.7 per cent monocytes. A second count was substantially similar. The Kahn reaction was negative. The sedimentation rate was 20 mm. per hour. The sputum has always been positive for tubercle bacilli until recently—it is now negative at times.

Biopsy shows hyperplasia of the epidermis with some miliary abscesses, thickening of the connective tissue and a dense infiltrate about hair follicles and blood vessels, with many abscesses containing giant cells, epithelial, round and polymorphonuclear cells. One double-contoured cell was found after long search.

DISCUSSION

DR. A. W. STILLIANS: It took quite a while for me to persuade the men at the sanitarium that it was safe to give iodides at all. We were unable to affect the blastomycosis until treatment with the iodides was started. The patient has never been able to take more than 15 grains (1 Gm.) of sodium iodide three times a day because of nausea. I wonder whether the iodides were really responsible for his loss of weight in the two months before streptomycin was used. He was losing weight before he came in. After the streptomycin was started he made rapid improvement and is still gaining, five months after the discontinuance of streptomycin. I am wondering whether some of the blastomycetes in this area may not be of mild virulence, for in recent years I have seen several cases with internal involvement that yielded to mild dosage. The diagnosis of pulmonary tuberculosis was made both on the roentgenologic and physical findings and on examination of the sputum. The patient has had a positive sputum until recently. Now he has occasional negative sputum.

NOTE: Since the meeting I have noted the report in *Science (Science* **108**:501 [Nov. 5] 1948) of the successful treatment of tuberculous guinea pigs with iodides and streptomycin.

Roentgen Dermatitis of the Scalp Following Therapy for Epilation. Presented by DR. D. V. OMENS and (by invitation) DR. H. OMENS and DR. D. MUSGRAVE.

E. H., an 8 year old white girl, has a history of having had tinea capitis, treated with roentgen ray epilation in November 1945. After the treatment there was an inflammatory bullous reaction, and in about three weeks there was complete loss of hair. There was a gradual regrowth of hair around the suboccipital and parietal areas.

On examination, there is seen to be complete alopecia of the vertex and occipital areas of the scalp, with atrophy, pigmentation and telangiectasia.

DISCUSSION

DR. I. M. FELSHER: This case is instructive because it emphasizes caution in roentgen epilation. It was rumored that 800 r were given by accident as an epilation dose at one time and that the hair returned normally. Nevertheless, it

is important to restrict the dose to the range of 350 to 400 r. I have often noticed that the hair returned more slowly after epilation in the areas where there was overlapping. Of course I do not know what error was committed in the treatment of this patient. Since I began the use of 5 per cent salicylanilide ointment I have resorted less frequently to roentgen epilation. If one can get the patient and the parents to cooperate diligently in the treatment with this ointment, cures can be expected within three to six months for the majority of patients. If such good results can be obtained in that period it is not necessary to resort to roentgen therapy. I have reached this conclusion after having done over 1,100 roentgen ray epilations without a single mishap of the type presented in this patient.

Extensive Carcinoma of the Wall of the Chest. Presented by DR. THEODORE CORNBLEET and (by invitation) DR. D. COHEN and DR. S. BARSKY.

DISCUSSION

DR. FRANCIS W. LYNCH, St. Paul, Minn.: Cancer of the breast can involve the skin in a variety of forms, but this case is interesting and unusual. Disseminated distant metastases in the skin are not all all uncommon. Neither is local direct extension to the skin. Continuous and more diffuse involvement is seen much less frequently. When such involvement spreads rapidly, there is redness and firm swelling which has many of the features of inflammation and is thus spoken of as erysipelas-like involvement. When the process is more chronic and deeper, it is spoken of as cancer en cuirasse, but I do not think this term should be applied to the less diffuse and more discrete involvement which is evident in this case. Some years ago Dr. C. D. Freeman Sr. and I had the opportunity to study a somewhat similar eruption of a patient who was on Dr. Madden's service at Ancker Hospital. In that instance the lesions were true vesicles with fluid content, and the linings of the cystic spaces showed the presence of cancer cells. In Dr. Cornbleet's case the lesions resemble vesicles, but I did not assure myself that they contained fluid. A microscopic section will be interesting.

In cases like this there is faint resemblance to the condition described by Bloodgood as comedocarcinoma. He used the term comedo in a different sense than the dermatologic one, applying it in a group of cases in which the cut surface of the tumor showed cystic lesions whose contents separated in the manner of a comedo. This condition would not easily be confused with that seen in Dr. Cornbleet's case.

DR. THEODORE CORNBLEET: I think it would take a careful postmortem dissection to prove absolutely that this condition is carcinoma en cuirasse. Nevertheless, the nodular growth elements are in linear alignment and would be difficult to visualize as developing otherwise than along lymphatics. Furthermore, the thorax is covered as a solid phalanx with this hard growth, while the skin of no other part of the anatomy is involved. It seems hardly possible that metastasis propagated via the blood stream would confine itself in this manner and escape all other parts.

Residual Lesions of Dermatitis Herpetiformis and Thyrotoxicosis in a Woman Aged 24. Presented by DR. HERBERT RATTNER and (by invitation) DR. H. RODIN and DR. S. BARSKY.

DISCUSSION

DR. H. RODIN (by invitation): When this patient was first seen in the clinic she had dermatitis herpetiformis and a classic textbook picture of thyrotoxicosis. We referred her to the surgical department where, in preparation for thyroidectomy,

potassium iodide was prescribed, with immediate improvement of the dermatitis herpetiformis. This treatment is so contrary to standard teaching that we thought it of sufficient interest to present the patient before the society. We do not think that the thyrotoxicosis had anything to do with the dermatitis herpetiformis.

Gangrena Hysterica (Neurotica). Presented by DR. MAURICE OPPENHEIM and DR. JAMES HERBERT MITCHELL.

Rosacea-like Tuberculid. Presented by DR. F. E. SENEAR and STAFF.

Lupus Vulgaris: Improvement After Treatment with Vitamin D_2. Presented by DR. JAMES R. WEBSTER and (by invitation) DR. HILBERT MUELLER and DR. OLIVER RIAN.

Arsenical Keratoses and Squamous Cell Epitheliomas. Presented by DR. F. E. SENEAR and STAFF.

Necrobiosis Lipoidica Diabeticorum with Cutaneous Lesions Preceding Diabetes by One Year. Presented (by invitation) by DR. LOUIS RUBIN.

Leg Ulcer with Sickle Cell Anemia in a Negro Girl Aged 18. Presented by DR. THEODORE CORNBLEET and (by invitation) DR. D. COHEN and DR. D. MUSGRAVE.

A Case for Diagnosis (Anagenital Lymphogranuloma Inguinale?). Presented by DR. THEODORE CORNBLEET and (by invitation) DR. H. SCHORR and DR. D. MUSGRAVE.

A Case for Diagnosis (Follicular Keratotic Lesions on Extremities). Presented by DR. THEODORE CORNBLEET and (by invitation) DR. D. COHEN and DR. D. MUSGRAVE.

Blastomycosis of the Wall of the Chest. Presented by DR. D. V. OMENS and (by invitation) DR. H. OMENS and DR. D. MUSGRAVE.

Granuloma Annulare. Presented by DR. D. V. OMENS and (by invitation) DR. H. OMENS and DR. S. BARSKY.

Cutaneous Pads on Fingers, Resulting from Biting? Presented by DR. THEODORE CORNBLEET and (by invitation) DR. D. COHEN and DR. S. BARSKY.

Giant Follicular Lymphoma (Brill-Symmers' Disease). Presented by DR. THEODORE CORNBLEET and (by invitation) DR. H. SCHORR and DR. S. BARSKY

A Case for Diagnosis (Generalized Lichen Planus? Tinea of Crural and Axillary Areas?). Presented by DR. THEODORE CORNBLEET and (by invitation) DR. H. SCHORR and DR. D. MUSGRAVE.

Pachyonychia Congenita, Epidermolysis Bullosa, Ectodermal Defect of Hair and Teeth in a Man Aged 29. Presented by DR. HERBERT RATTNER and (by invitation) DR. H. RODIN and DR. S. BARSKY.

Incapacitating Plantar Hyperkeratoses (Multiple Verrucae). Presented by DR. THEODORE CORNBLEET and (by invitation) DR. H. SCHORR and DR. S. BARSKY.

DETROIT DERMATOLOGICAL SOCIETY

Charles Reyner, M.D., *Chairman*

Hermann Pinkus, M.D., *Recorder*

Oct. 19, 1948

Lichen Nitidus (with Koebner's Phenomenon). Presented by DR. JOHN N. GREKIN.

S. S., a Negro boy 6 years old, shows minute skin-colored or lighter, somewhat shiny papules of pinhead size and smaller. These are widely distributed on the trunk, extremities and penis and are often grouped. There is pronounced accentuation over knees and elbows. In both these areas linear distribution of the papules can be seen, as in Koebner's phenomenon.

These lesions were noted for the first time in July 1948, and the number of papules increased up to one month before presentation. After that time no increase was seen.

There is no history of pertinent previous diseases. There is tuberculosis in the father's family, and the child has been exposed.

Roentgenologic examination of the chest showed no pathologic changes. Biopsy of several papules showed typical lichen nitidus.

DISCUSSION

DR. JOHN N. GREKIN: I have been unable to find a reference in the literature to the occurrence of this linear arrangement of the papules in lichen nitidus. It certainly suggests the possibility of some relation between lichen nitidus and lichen planus. This possibility has been suggested by various writers in the past.

DR. HERMANN PINKUS, Monroe, Mich.: I had never seen a similar distribution until a few weeks ago, and I shall bring my patient to one of the future meetings. She is a 4 year old Negro girl with widespread eruption of typical lichen nitidus. Some of the lesions are arranged in lines, particularly near the elbows, just as in Dr. Grekin's case. In addition, lesions form a broad band down the flexor surface of the right thigh, as in lichen striatus. Felix Pinkus was inclined to think that the first change in lichen nitidus is a degeneration of some basal cells which provokes the granulomatous reaction in the corium. Damage of the basal layer also is an early and constant sign in lichen planus. So there is histologic as well as clinical similarity.

Lupus Tumidus and Tuberculosis Colliquativa Involving the Neck. Presented by DR. LOREN W. SHAFFER and DERMATOLOGY STAFF, City of Detroit Receiving Hospital.

Sarcoid of Boeck in a Negro Woman Aged 31. Presented by DR. LOREN W. SHAFFER and DERMATOLOGY STAFF, City of Detroit Receiving Hospital.

Boeck's Sarcoid (Unusually Widespread Form) in a Negro Woman Aged 44. Presented by DR. LOREN W. SHAFFER and DERMATOLOGY STAFF, City of Detroit Receiving Hospital.

DISCUSSION OF CASES OF TUBERCULOSIS AND SARCOID

DR. JOHN R. KING (by invitation): The younger woman with sarcoid and the woman with lupus tumidus and an old case of tuberculosis colliquativa show definite improvement on treatment with low doses of vitamin D_2. It is true that sarcoid often undergoes involution spontaneously, but the younger patient with sarcoid is a woman whose disease dates back one year and whose improvement was pronounced on this therapy. It is interesting to note that her skin lesions have disappeared while the pulmonary picture remains unchanged. The condition of the woman with lupus tumidus and tuberculosis colliquativa is better than it has been in thirty years, showing 50 per cent improvement in a matter of months. These results have both been obtained on low doses where one rarely sees any evidence of toxicity.

DR. DONALD BOERSMA, Grand Rapids, Mich.: Initial improvement in sarcoid usually is good, but to get a complete cure is difficult.

DR. L. W. SHAFFER: The condition of the older woman with sarcoid is unusually extensive. The atrophy and scaling present at the sites of previous infiltrative lesions give a picture somewhat suggestive of syphilis or mycosis fungoides. In spite of the extensive cutaneous involvement the patient's general health appears good, there are no bone lesions and pulmonary lesions are minimal or absent.

DR. DONALD BOERSMA, Grand Rapids, Mich.: When do you use calciferol, when drisdol® solution, and when dihydrotachysterol?

DR. R. H. GREKIN, Ann Arbor, Mich. (by invitation): Epithelioid cells have been shown to be a response to phospholipids. Since the basic pathologic cell of lupus vulgaris and sarcoidosis is the epithelioid cell, it was reasoned that calciferol

(vitamin D_2, irradiated ergosterol) would be beneficial in treatment of sarcoidosis as well as lupus vulgaris. This proved to be the case, but patients with sarcoidosis did not tolerate calciferol very well. Calciferol acts primarily on the absorption of calcium, with a resultant elevation of serum calcium and increased excretion of phosphorus. Dihydrotachysterol, which is a breakdown product of irradiated ergosterol, has its major action on the excretion of phosphorus and only a minor action on the absorption of calcium. It is the phosphorus from the phospholipids we are trying to get rid of, and dihydrotachysterol proved as effective as calciferol, with less toxic reactions. Drisdol® solution is simply calciferol in solution in propylene glycol. It permits a lower but less accurate dose. Vitamin D_3 (irradiated 7-dehydrocholesterol) has not been tried as yet. It is possible that it will not be as toxic as calciferol. Parathyroid injection acts solely on the excretion of phosphorus. However, this must be given by injections and is quite expensive.

Pringle's Disease (Adenoma Sebaceum) in a Negro Aged 40. Presented by DR. LOREN W. SHAFFER and DERMATOLOGY STAFF, City of Detroit Receiving Hospital.

DISCUSSION

DR. HERMANN PINKUS, Monroe, Mich.: The microscopic picture of this case shows angiofibromas rather than sebaceous adenomas. This observation is the rule in my experience. In 7 cases which I have had the opportunity to study microscopically, I have never seen anything which could be termed adenomatosis or even hypertrophy of the sebaceous glands. Occasionally I had the impression that there was an increased number of hair follicles; the sebaceous glands, if affected, were atrophic, and so-called *Mantelhaare* (cloaked hairs) were often seen. I believe that Pringle mistook the normally large sebaceous glands of the central part of the face for adenomas and that some other observers have repeated his mistake. It is generally agreed that the "shark skin" plaques and the paronychial and gingival tumors of these cases are connective tissue lesions. On the face, as on other parts of the skin and in other organs of the body (with the exception of the brain), the tumors in Pringle's disease are of mesodermal rather than ectodermal origin, and the term "adenoma sebaceum" is a misnomer.

DR. ARTHUR E. SCHILLER: What name would you use?

DR. HERMANN PINKUS, Monroe, Mich.: Pringle's disease, or epiloia, the term which has been accepted for the fully developed syndrome of cutaneous tumors and tuberous sclerosis of the brain. The woman who was presented before this Society at Eloise Hospital in 1937 (ARCH. DERMAT. & SYPH. **38**:314 [Aug.] 1938) had acquired fibroids of the uterus with sarcomatous degeneration when she was presented again in 1947 (unpublished).

Reticulogranuloma (Letterer-Siwe Disease with Reticulogranulomatous Skin Tumor). Presented by DR. HERMANN PINKUS, Monroe, Mich.

W. B., a white boy 16 months old, acquired a rash on the scalp, a sore under the right arm and a sore mouth at about the same time in July 1948. Examination on Aug. 11, 1948, revealed a rather thin child with bluish mottled skin and somewhat distended abdomen. The scalp was covered with crusts and fine scales through which some red papules could be seen. The oral mucosa was covered with thick white membranes. In the right axilla was a dime-sized, button-like, firm, flat nodule with eroded necrotic surface. A diagnosis of generalized moniliasis was considered, but Candida was not found in smears or cultures from the mouth. The condition of the mouth improved under swabbing with methylrosaniline chloride

(gentian violet) solution, and that of the scalp, under treatment with strong mercurial ointment U.S.P. The appetite improved and the baby gained some weight during the next five weeks but had an intermittent fever, with temperatures up to 102 F. The lesion in the axilla remained unchanged and was removed surgically October 6. It was diagnosed by a general pathologist as reticulum cell lymphosarcoma. Microscopic examination showed a granulomatous lesion composed of large pale reticulum cells. There was a liberal sprinkling of eosinophilic leukocytes. The picture was that of the lesions of the skin seen in cases of benign localized reticulogranuloma (so-called eosinophilic granuloma) of bone.

Meanwhile the baby has received several blood transfusions. He has acquired crops of petechial skin lesions, and the eruption on the scalp is more plainly papular. Roentgenologic studies of the skeleton revealed no definite evidence of destructive bone lesions. Liver and spleen are not definitely enlarged.

DISCUSSION

DR. STANLEY J. JOYCE: This child presents an excellent picture of reticulogranuloma. The etiology of this disease is unsettled. A metabolic disturbance with fatty deposits into reticuloendothelial cells is uniformly found. Any one organ or a combination of organs containing such tissues may be involved. As in the patient presented, the picture on the skin and mucous membrane may simulate a seborrheic dermatitis, a moniliasis or an exudative erythema multiforme with or without petechiae.

This disease has been discussed under various names, depending on the principal organ or combination of organs involved and the extent of involvement. The principal names are xanthomatosis, reticuloendotheliosis, cholesterosis, Hand-Schüller-Christian disease (skull, long bones, diabetes insipidus, exophthalmos, abnormal growth), Gaucher's disease (spleen, liver, long bones, skin), Niemann-Pick (liver, spleen, skin), eosinophilic granuloma, Letterer-Siwe and Bürger-Grütz diseases.

The case of a boy seen by me started with an extensive exudative eczema at the age of 6 weeks. The disease continuously increased until the patient's death at the age of 15 months, at which time the condition extensively involved the lungs, lymph nodes, bones, spleen and skin. In the meantime, the child had a spontaneous fracture of the right humerus in a rarified area. The skull and jaw bones were also invaded. There was an inflammatory hypertrophy of the gingivae and disturbance of the development and eruptions of the teeth. The course of the disease included secondary infections of the lungs, oral cavity and ears and decided undernutrition.

DR. HERMANN PINKUS, Monroe, Mich.: I presented this case under the designation of reticulogranuloma because it appears timely to choose a generic new name for the group of diseases to which Letterer-Siwe disease, lipid granulomatosis (including the Hand-Schüller-Christian syndrome) and so-called eosinophilic granuloma of bone belong. The last named might be better designated as benign or localized reticulogranuloma because eosinophilic cells are not an essential feature and because the word "eosinophilic granuloma" is also used for probably entirely unrelated miscellaneous skin lesions. (Pinkus, Copps, Custer and Epstein, *Am. J. Dis. Child.* **77**:503 [April] 1949.) These cases are often diagnosed on biopsy as reticulum cell sarcoma, but while the prognosis certainly is poor in young babies, more and more cases become known in which the children not only survive, but recover completely.

Syphilitic Hepatitis. Presented by DR. LOREN W. SHAFFER and DERMATOLOGY STAFF, City of Detroit Receiving Hospital.

DISCUSSION

DR. LOREN W. SHAFFER: The liver was greatly enlarged, as may be seen from the photograph showing its original outline. Therapy offers a problem since the therapeutic paradox of too rapid healing could readily produce portal obstruction. The patient has been treated with mercuric succinimide, .004 Gm. twice weekly, given intramuscularly, plus potassium iodide administered by mouth. Recently treatment with the mercury preparation has been stopped and administration of bismuth subsalicylate, .02 mg. at weekly intervals, substituted. The liver has shrunk about 3 fingerbreadths, below the costal margin, and the patient feels well. We are pleased rather than disappointed with the slow improvement and will continue treatment with the bismuth compound and potassium iodide. We believe that arsenic or penicillin therapy is definitely contraindicated.

Arsenical Keratoses and Carcinoma of the Heel in a Patient with Mild Psoriasis. Presented by DR. EUGENE A. HAND, Saginaw, Mich.

DISCUSSION

DR. EUGENE A. HAND, Saginaw, Mich.: Arsenic was used in medicine in the Hippocratic era and has been popular as a poison at least since the fourteenth century. Rousselot (cited by Bechet, P. E.: ARCH. DERMAT. & SYPH. **23**:110 [Jan.] 1931) in 1769 mentioned the use of arsenic paste in the treatment of cancer. Girdlestone (*London Med. & Phys. J.* **15**:297 [April] 1806) in 1806 advised the use of potassium arsenite (Fowler's) solution in leprosy, psoriasis and lichen prurigo, and also, along with mercury, for syphilis. Devergy recognized melanosis from arsenic in 1857. Pozzi (*Bull. Soc anat. de Paris,* **9**:587, 1874) reported warty growths on the palms and soles which developed into carcinoma of the foot in a person with psoriasis. White (*Am. J. M. Sc.* **89**:163, 1885) in 1885 first reported the syndrome of keratosis and cancer from treatment of psoriasis with arsenic.

Nutt, Beattie and Pye-Smith (*Lancet* **2**:210 [July 26]; 282 [Aug. 2] 1913) reviewed this syndrome in 1913 and added 1 case of their own. In 31 cases they found 19 patients with lesions on the hands and fingers, 5 with them on the feet, including the toes, 3 with involvement of the scrotum, 2 with lesions on the pubic area, including 1 woman with a vulvar lesion, and several with cancers on the back and trunk. In 12 there developed metastases, and 16 died of cancer. Most of the growths were of the squamous cell type, though Hutchinson mentioned several basal cell ones. The sex incidence was 3 men to 1 woman.

DR. LOREN W. SHAFFER: I have never seen arsenical keratoses develop after treatment with the organic arsenicals such as arsphenamine, neoarsphenamine or oxophenarsine hydrochloride (mapharsen®) in which the arsenic is trivalent, or tryparsamide or phenarsone sulfoxylate (aldarsone®), in which it is pentavalent. The potentialities for the development of keratoses and carcinoma from arsenical drugs therefore seem to depend on the organic or nonorganic classification of the drug rather than on the valence of the arsenic.

DR. J. COURVILLE: Organic arsenicals cause exfoliative dermatitis and damage to vascular structures; inorganic arsenic compounds act on the epidermis.

DR. EUGENE A. HAND, Saginaw, Mich.: Most of the references to this syndrome in the literature refer to potassium arsenite solution, arsenious acid solution and

(Donovan's) solution of arsenic and mercuric iodides. Asiatic pills (arsenic trioxide and black pepper, in varying amounts, according to the formula), seem less likely to cause this. Pentavalent arsenic has a special affinity for ectodermal structures such as epidermis, sweat and sebaceous glands, ducts, hair and hair follicles, and a very slight affinity for the blood vessels of the corium. It causes melanosis, keratoses, cancer, polyneuritis and optic atrophy. The organic compounds containing pentavalent arsenic such as atoxyl (sodium arsanilate) and tryparsamide, are rapidly excreted and do not cause keratosis, cancer or melanosis, though they do cause optic atrophy. Perhaps Asiatic pills are also excreted rapidly with minimal absorption.

Lymphoblastoma (Lymphosarcoma? Lymphocytoma?) Presented (by invitation) by DR. J. L. COHEN, Windsor, Ontario, Canada.

Lymphoblastoma (So-Called Spiegler-Fendt Sarcoid). Presented by DR. HARTHER L. KEIM.

HAWAII DERMATOLOGICAL SOCIETY

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Nov. 6, 1948

Scleredema Adultorum (Piffard-Buschke). Presented by DR. E. K. CHUNG-HOON, Honolulu.

M. M., a 38 year old Puerto Rican housewife, was admitted to St. Francis Hospital on March 9, 1947, with a diagnosis of acute rheumatic fever. She had been ill with sore throat, painful and swollen ankle and knee joints and dysphagia for less than a week. On the ninth hospital day she acquired edema of the neck, firm and nonpitting in character, which spread rapidly over the shoulders and arms and chest and upward onto the face. The skin was firm and tight and could not be grasped between the fingers. No pigmentation was noted, and no dermatitis. The rheumatic symptoms subsided under salicylate therapy, and the patient was discharged on May 14. Only slight improvement has occurred in the lesions of the skin (she can open her mouth more widely) since their onset twenty months ago. The hands and feet have never been involved, and no atrophy has occurred.

Examination of a deep biopsy specimen of the involved area and the underlying muscle revealed broadening and separation of the collagen fibrils in the deeper portion of the corium. No other changes were noted, and the muscle appeared normal.

DISCUSSION

DR. HARRY L. ARNOLD JR., Honolulu: It is interesting that Buschke usually gets the credit for first describing this disorder, whereas actually Piffard described it first in his atlas, a few years previously. I believe this long duration of symptoms—twenty months—is exceptional.

DR. HAROLD M. JOHNSON, Honolulu: I would suggest that tocopherols be tried, say 50 to 100 mg. a day, for a period of time because of the effect on collagen which has been described recently by Burgess (ARCH. DERMAT. & SYPH. **59**:605-614 [April] 1948).

DR. NICHOLAS STEUERMAN, Eleele, Kauai (by invitation): I should like to suggest a trial of "A.T. 10," dihydrotachysterol; I have seen it produce great benefit in scleroderma, and I think it might, by analogy, be helpful in this condition as well.

DR. HARRY L. ARNOLD JR., Honolulu: The process in scleroderma is quite different from that in scleredema, really; still, dihydrotachysterol might be worth a trial.

DR. E. K. CHUNG-HOON, Honolulu: I was interested in the past history. it was lengthy. The patient had had repeated infections throughout her life; in childhood she had had tonsillitis, and, at the age of 14, after another attack, she had had her tonsils removed. Then she had had sinusitis and otitis media; then, in early adult life, gonorrhea, and at about that time, an appendectomy and sterilization. At the onset of the present illness she had a picture of what was presumed to be acute rheumatic fever, swollen ankles and knees and multiple joints being involved, with a temperature of 104 F. Then she was admitted to the hospital and about nine days later acquired the solid edema of the neck and face. Was the joint involvement part of the scleredema adultorum, or was it actually a manifestation of acute rheumatic fever? A cardiac consultant was called to see the patient; in fact, she was admitted to the cardiac clinic. However, on review of the case the cardiologist in charge of the clinic expressed the belief that, while this patient had all the symptoms and some of the findings of rheumatic heart disease, only a tentative diagnosis of rheumatic heart disease should be made. He was of the opinion that the rheumatic fever had in some way a connection with the collagen disease.

DR. HARRY L. ARNOLD JR., Honolulu: Most cases of this disease have followed some relatively minor acute infection, and several reported cases have followed rheumatic fever. But just as many have followed ordinary tonsillitis, or sore throat, or influenza, or anything of that sort. A case that I reported in 1939 followed tuberculous cervical lymphadenitis.

Adenoma Sebaceum (Bourneville-Pringle). Presented by DR. HAROLD M. JOHNSON, Honolulu.

C. F., a white girl aged 4, had been in good health until the age of 2 years when she suddenly had severe convulsive seizures. These were thought to have been precipitated by whooping cough immunization. Several months later a similar convulsion occurred without any "trigger" cause. This attack lasted several hours.

During the last nine months small punctate, salmon red macules and papules have appeared on the malar surfaces, the bridge of the nose and the forehead. Recently several new small papules were noted on the neck. There is a slight increase of erythema and itching of the face after long exposure to the sun.

Several complete blood counts were within normal range. Roentgenograms of the skull showed two areas of calcification which appear to be located in the region of the glomus of the choroid plexus and not in the cerebral tissue. A possible area of calcification may be present in the cortex of the brain.

The child's intelligence quotient is well above average.

DISCUSSION

DR. HARRY L. ARNOLD JR., Honolulu: Dr. Johnson and I had agreed on a tentative diagnosis of early discoid lupus erythematosus in this case until the history of convulsions was obtained, and it was then that he made the diagnosis—with which I concur completely—of adenoma sebaceum. Of course, these lesions are neither adenomatous nor sebaceous; they are fibrovascular. Perhaps Pringle's disease is the most suitable name for them in the light of our present ignorance.

DR. HAROLD M. JOHNSON, Honolulu: This case impresses me as a variant of the usual pattern: it has not the triad of epiloia, since there is no mental deterioration and no pineal calcification. Mental deterioration may develop at a later date.

DR. HARRY L. ARNOLD JR., Honolulu: Perhaps the appearance of these lesions could be improved a good deal by extremely meticulous and gentle electrodesiccation of a few at a time, with the patient under light general anethesia.

Lichen Amyloidosis. Presented by DR. NICHOLAS STEUERMAN, Eleele, Kauai (by invitation).

Mrs. S., a 28 year old Japanese housewife, first noticed a small area of hyperpigmentation on the right shin during her first pregnancy, six years ago. After delivery this area began to itch intermittently; it slowly spread. Two years ago, after the birth of her third child, a similar lesion appeared on the left shin, and shortly after this a diagnosis of circumscribed neurodermatitis was made. Treatment was ineffective. A fourth pregnancy neither aggravated nor alleviated the condition. A month before presentation a specimen for biopsy was removed, the examination being reported by Dr. Hermann Pinkus as showing amyloidosis cutis. After the removal of tissue for biopsy, it was observed that the itching remained greatly diminished and the lesions distinctly flatter and paler in the area, which measured about 4 by 8 cm., that had been infiltrated with procaine hydrochloride (novocain®). The remainder of the lesion still manifested the profuse eruption of discrete, close-set, rough, grayish brown papules, 2 to 3 mm. in diameter. A second area was infiltrated with procaine hydrochloride, 1.5 per cent, and likewise manifested slight but distinct subjective and objective improvement.

DISCUSSION

DR. HARRY L. ARNOLD JR., Honolulu: Spontaneous involution has been reported in this disorder, but the improvement shown by this patient certainly looks as if it had been produced by the injections of procaine. I agree with Dr. Steuerman, and with the patient, that the treatment is worth trying in a few more areas. Also, as long as tocopherols are being tried in so many disorders, here is another mysterious connective tissue disorder in which they might be worth a trial.

Tuberculoid Leprosy. Presented by DR. E. K. CHUNG-HOON, Honolulu.

K. K., a Japanese woman aged 58, first noted numbness of the right foot about a year ago followed shortly thereafter by a pink papular rash on the left leg. Gradually the skin of the right arm and then other parts of the body became involved. The eruption resembled an attack of hives, but there was no itching and the eruption did not fade. Various remedies were tried, but to no avail, and when the eruption appeared on her face the patient consulted a physician. As the lesions of the skin became large and more vivid in color she noticed crawling sensations of the forehead and also of the lesions of the body and extremities.

There is a generalized eruption consisting of annular lesions with raised pink borders and depressed skin-colored centers. Where the lesions are heavy, as on the face, they have coalesced into large pink plaques. The uninvolved skin between lesions is apparently normal in texture. Ulnar and great auricular nerves are palpable but of average size. No pareses were noted at this time. There is thermal and tactile anesthesia in the lesions.

Histopathologic Picture.—The epidermis is thin and normal in appearance although the basal layer contains an unusually large amount of melanin. In the upper, papillary part of the corium there are a number of very small streaks and foci of cellular infiltrate which are made up almost entirely of lymphocytes and plasma cells. These are concentrated about cutaneous appendages and small blood vessels. No definite nerve involvement can be found. Examination of a stained section revealed no acid-fast organism.

DISCUSSION

DR. HARRY L. ARNOLD JR., Honolulu: I should like to comment on the classification there. The lesions were histologically indeterminate, not tuberculoid, and the British leprosy workers, especially Ryrie, the editor of the *Leprosy Review*, have bitterly criticized the category of indeterminate leprosy. Ryrie stated that all it is characterized by is "the possession of a histological rejection slip," and that it isn't histologically lepromatous and it isn't histologically tuberculoid, but I think that this case is a good illustration of the fact that that contention is not true. It is just a wisecrack, and the point is not well taken. This case is not histologically tuberculoid, and yet I agree with Dr. Chung-Hoon that it is tuberculoid leprosy, that it is the type in which there is a good defensive reaction against the disease, with no bacilli present in the lesions histologically and a positive—not a strongly positive, but still a positive—Mitsuda reaction, with correspondingly a rather good prognosis, even better, of course, under treatment. I think it is a very instructive case from that standpoint, i. e., that the word tuberculoid does not mean histologically tuberculoid but biologically tuberculoid.

DR. E. K. CHUNG-HOON, Honolulu: It is also possible for one lesion on an extremity to show nonspecific changes and for a lesion elsewhere to show the tuberculoid picture. So perhaps this difference may be a difference in stage. We have seen typical tuberculoid cases, when the process regresses to complete clearing or to hypopigmentation with no clinical infiltration, show a nonspecific inflammatory type of histologic picture. The case was also presented as a matter of interest in therapy. In the acute phase, we decided to give the patient promin®. For this patient I chose promin® (sodium p,p'-diaminodiphenylsulfone-N,N'didextrose sulfonate) because it causes headache less often than does diasone® (disodium formaldehyde sulfonylate diaminodiphenylsulfone). I gave her 0.5 Gm. daily intravenously for one week, then stepped the dose up to 1 Gm. daily for another week and then increased it from there on by 1 Gm. until she was taking 4 Gm.; so it took me about a month to get her dose up to 4 Gm., and then I gave her a rest period for one week. Then our plan is to continue three weeks of therapy at 4 Gm. a day with one week rest. The cycle is repeated until we feel that clinical regression has occurred. Then we discontinue treatment.

The interesting part about this case demonstrated what I have seen in a large percentage of the cases in which a sort of Herxheimer-like reaction occurs within three or four weeks of the initiation of therapy—and so it happened in her case. During the rest week, the lesions started to flare a little bit and become even more noticeable than they were in the beginning, definitely elevated and reddish pink; the patient's whole face was flushed from the coalescence of these annular lesions. We thought the reaction was just the typical thing we had been seeing and that it would go down as in other cases, and so we started treating the patient again with 4 Gm. when she was due to resume therapy. On the second day there developed an erythematous papular and scarlatiniform eruption which started on the chest and extremities and soon became generalized and extremely pruritic. I interpreted this as a drug eruption and cut off administration of the medicine; the leprous lesions flared even more, and so I gave the patient some diphenhydramine (benadryl®) and ointment to rub on, and the eruption gradually faded. In four or five days she had clearing and all the leprosy lesions cleared up to the point that they are today, becoming hardly visible except in bright light. Then we gave the patient 0.5 Gm. of promin,® and about the second day there was a flare again. Then she had the drug eruption again with a lot of pruritus, and so we stopped administration of the medicine. Thus it has been about a week or ten days since

she has had any medication. I suppose that the case is promin®-sensitive. It might be interesting to switch treatment to administration of diasone.® I feel that the patient needs more therapy.

DR. HAROLD M. JOHNSON: She is living at home?

DR. E. K. CHUNG-HOON: Yes, she comes in as an outpatient for treatment.

DR. HARRY L. ARNOLD JR.: I am delighted to see outpatient treatment of leprosy being carried on now, as it is working out so well in Mexico that I feel we can develop it successfully here. It should go a long way toward reducing general fear of the disease, by eliminating the long period of incarceration.

A Case for Diagnosis (Disseminated Discoid Lupus Erythematosus?). Presented by DR. HARRY L. ARNOLD JR., Honolulu.

Adenocarcinoma of Stomach, Metastatic to Skin. Presented by DR. HAROLD M. JOHNSON, Honolulu.

Chronic Disseminated Lupus Erythematosus. Presented by DR. HARRY L. ARNOLD JR., Honolulu.

Pemphigus Erythematosus (Senear-Usher). Presented by DR. HARRY L. ARNOLD JR., Honolulu.